DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 24-25, 2015
Atlanta, Georgia

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30333
June 24-25, 2015

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 24th			
8:00	**Welcome & Introductions**		Dr. Jonathan Temte (ACIP Chair) Dr. Cindy Weinbaum (Acting Executive Secretary, ACIP; CDC/NCEZID)
8:30	**Meningococcal Vaccines**		
	Introduction		Dr. Lorry Rubin (ACIP, WG Chair)
	GRADE: evidence for use of MenB vaccine in adolescents and college students	Information & Discussion	Dr. Temi Folaranmi (CDC/NCIRD)
	Considerations for routine use of MenB vaccines in adolescents		Ms. Jessica MacNeil (CDC/NCIRD)
10:15	Public Comment - Meningococcal Vaccines		
10:45	***Break***		
11:00	**Meningococcal Vaccines**		
	Proposed recommendations	**Vote**	Ms. Jessica MacNeil (CDC/NCIRD)
	VFC Vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
11:30	**General Recommendations on Immunization**		
	Introduction	Information & Discussion	Dr. Marietta Vàzquez (ACIP, WG Chair)
	Various topics		Dr. Ray Strikas (CDC/NCIRD)
	Proposed recommendations	**Vote**	Dr. Ray Strikas (CDC/NCIRD)
12:45	***Lunch***		
2:00	**Novel Influenza Vaccines**		
	Introduction	Information & Discussion	Dr. Doug Campos-Outcalt (ACIP, WG Chair)
	Influenza A (H5) epidemiology update		Dr. Sonja Olsen (CDC/NCIRD)
2:45	**Influenza**		
	Introduction		Dr. Ruth Karron (ACIP, WG Chair)
	Influenza vaccine effectiveness update	Information & Discussion	Dr. Brendan Flannery (CDC/NCIRD)
	Quadrivalent intradermal influenza vaccine		Dr. Corey Robertson (Sanofi Pasteur)
	Influenza vaccine safety update		Dr. Tom Shimabukuro (CDC/NCEZID)

	High dose influenza vaccine update		Dr. Lisa Grohskopf (CDC/NCIRD)
	Proposed recommendations	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
4:15	***Break***		
4:30	**Smallpox Vaccine: Use in Laboratory Personnel**		
	Introduction	Information & Discussion	Dr. Lee Harrison (ACIP, WG Chair)
	Proposed smallpox vaccine recommendations	**Vote**	Dr. Brett Petersen (CDC/NCEZID)
5:15	**Public Comment**		
5:30	**Adjourn**		

Thursday, June 25th

8:00	**Agency Updates**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH	Information	CDC and *ex officio* members
8:15	**Japanese Encephalitis Vaccine**		
	Japanese Encephalitis Vaccines Work Group update	Information	Joseph Bocchini (ACIP, WG Chair)
8:20	**Pneumococcal Vaccines**		
	Introduction	Information & Discussion	Dr. Nancy Bennett (ACIP, WG Chair)
	Intervals between PCV13 and PPSV23: supporting evidence and rationale for change		Dr. Miwako Kobayashi (CDC/NCIRD)
	Proposed recommendations	**Vote**	Ms. Tamara Pilishvili (CDC/NCIRD)
9:20	***Break***		
9:35	**Combination Vaccines**		
	Formation of Combination Vaccines Work Group	Information & Discussion	Dr. Art Reingold (ACIP, WG Chair)
9:45	**Human Papillomavirus (HPV) Vaccines**		
	Introduction	Information & Discussion	Dr. Joe Bocchini (ACIP, WG Chair)
	9-valent HPV vaccination for persons who have completed an HPV vaccination series		Dr. Lauri Markowitz (CDC/NCHHSTP)
	Cost effectiveness		Dr. Harrell Chesson (CDC/NCHHSTP)
	Proposed guidance		Dr. Lauri Markowitz (CDC/NCHHSTP)

11:00	**Pertussis**		
	Introduction		Dr. Art Reingold (ACIP, WG Chair)
	Cocooning and Tdap vaccination	Information & Discussion	Dr. Jennifer Liang (CDC/NCIRD)
	Acellular pertussis vaccine effectiveness among children and adolescents in the setting of pertactin-deficient B. pertussis, Vermont, 2011-2013		Dr. Lucy Breakwell (CDC/NCIRD)
11:45	**Herpes Zoster**		
	Introduction		Dr. Ed Belongia (ACIP, WG Chair)
	Update on herpes zoster epidemiology and vaccine uptake	Information & Discussion	Dr. Rafael Harpaz (ACIP/NCIRD)
	Results of GSK Phase 3 study of investigational adjuvant-based zoster vaccine		Dr. Thomas Heineman (GSK)
12:45	**Public Comment**		
1:00	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention	**NCHHSTP**	National Center for HIV, Hepatitis, STD andTB Prevention [of CDC/OID]
CMS	Centers for Medicare and Medicaid Services	**NCIRD**	CDC National Center for Immunization & Respiratory Diseases [of CDC/OID]
DoD	Department of Defense	**NCEZID**	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
DVA	Department of Veterans Affairs	**NIH**	National Institutes of Health
FDA	Food and Drug Administration	**NVPO**	National Vaccine Program Office
GRADE	Grading of Recommendations Assessment, Development and Evaluation	**PCV13**	13-valent Pneumococcal Conjugate Vaccine
HPV	Human Papillomavirus	**PPSV23**	Pneumococcal Polysaccharide Vaccine
HRSA	Health Resources and Services Administration	**Tdap**	Tetanus, Diphtheria, and acellular Pertussis Vaccine
IHS	Indian Health Service	**VFC**	Vaccines for Children
MenB	Meningococcal B		

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
AE	Adverse Events
AFP	American Family Physicians
aHCST	Autologous Hematopoietic Stem Cell Transplant
AHIP	America's Health Insurance Plans
AMA	American Medical Association
ANA	American Nurses Association
ASTHO	Association of State and Territorial Health Officials
BMI	Body Mass Index
BIO	Biotechnology Industry Organization
BMBL	Biosafety in Microbiological and Biomedical Laboratories
CDC	Centers for Disease Control and Prevention
CEJA	Council on Judicial and Ethic Affairs, AMA
ChAd3-EBO Z	Chimpanzee Adenovirus 3-Based Vaccine
CICP	Countermeasures Injury Compensation Program
CIN	Cervical Intraepithelial Neoplasia
CISA Project	Clinical Immunization Safety Assessment Project
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Disease, AAP
CSAPH	Council on Science and Public Health, AMA
CSTE	Council of State and Territorial Epidemiologists
DMID	NIAID Division of Microbiology and Infectious Diseases
DoD	Department of Defense
DRC	Democratic Republic of the Congo
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
EBR	Evidence-Based Recommendations
EEOC	Equal Employment Opportunity Commission
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FLU VE	Influenza Vaccine Effectiveness Network
GBS	Guillain-Barré Syndrome
gE	Glycoprotein E
GMT	Geometric Mean Titer
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HD-IIV	High-Dose Inactivated Influenza Vaccine
HI	Hemagglutination Inhibition
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Serum Bactericidal Activity using Human Complement
HZ	Herpes Zoster
HZAC	HZ Adjudication Committee
HZO	Herpes Zoster Ophthalmicus
HZ/su	Herpes Zoster Adjuvanted Subunit Vaccine
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Poliomyelitis Vaccine
ISO	Immunization Safety Office
IT	Information Technology
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
LCI	Laboratory-Confirmed Influenza
LMP	Last Menstrual Period
LSU	Louisiana State University
MAARI	Medically Attended Acute Respiratory Illness

MATS	Meningococcal Antigen Typing System
MedDRA	Medical Dictionary for Regulatory Activities
MCV4	Meningococcal Conjugate Vaccine
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MenB	Serogroup B Meningococcal Disease
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MPL	Monophsophoryl Lipid
MSM	Men Who Have Sex With Men
mTVC	Modified Total Vaccinated Cohort
NACI	National Advisory Committee on Immunization, Canada
NEJM	*New England Journal of Medicine*
NIAID	National Institute of Allergy and Infectious Diseases
NAIP	National Adult Immunization Plan
NIP	National Immunization Program
NNDSS	National Notifiable Disease Surveillance System
NNV	Number Needed to Vaccinate
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NMA	National Meningitis Association
NNV	Number Needed to Vaccinate
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OAH	Office of Adolescent Health
OPM	Office of Personnel Management
OWM	Office of Women's Health
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PHN	Post-Herpetic Neuralgia
PIDS	Pediatric Infectious Diseases Society
pIMD	Potential Immune Mediated Disease
PMI	Precision Medicine Initiative
PRAMS	Pregnancy Risk Assessment Monitoring System
PREP Act	Public Readiness and Emergency Preparedness Act
PREVAIL	Partnership for Research on Ebola Vaccines in Liberia
PPSV	Pneumococcal Polysaccharide Vaccine
QALYs	Quality Adjusted Life Years
QIV-ID	Fluzone Intradermal® Quadrivalent Vaccine
QoL	Quality of Life
qPCR	Quantitative PCR
RA	Rheumatoid Arthritis
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAB	Spontaneous abortion
SAEs	Serious Adverse Events
SD-IIV	Standard-Dose Inactivated Influenza Vaccine
SHEA	Society for Healthcare Epidemiology of America
SIVAC	Supporting National Independent Immunization and Vaccine Advisory Committees
SPS	Shingles Prevention Study
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV-HD	Trivalent, Inactivated Influenza Vaccine
UK	United Kingdom
US	United States
USAMRIID	US Army Medical Research Institute of Infectious Disease
USPHP	United States Public Health Service
USPSTF	US Preventive Services Task Force
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VSVdeltaG-ZEBOV	Vesicular Stomatitis Virus-Based Vaccine
VFC	Vaccines for Children
VHA	Veterans Health Administration
VICP	Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization
WIR	Wisconsin Immunization Registry
YF	Yellow Fever
VLP	Virus-Like Particle
VZV	Varicella Zoster Virus

Welcome, Introductions, & Farewells

Welcome

Jonathan Temte, MD, PhD
ACIP Chair

Dr. Cindy Weinbaum
Acting Executive Secretary, ACIP / CDC

Following Dr. Temte's greeting and call to order, Dr. Weinbaum welcomed everyone to the June 2015 Advisory Committee on Immunization Practices (ACIP) meeting. She indicated that the proceedings of this meeting would be available to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She then recognized several others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Stephanie Thomas, Natalie Greene, Jean Smith, and Chris Caraway.

Dr. Weinbaum noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following this meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Ian Branam for assistance in arranging interviews.

The next ACIP meeting will convene at CDC on Wednesday and Thursday, October 21-22, 2015. Registration for all meeting attendees is required and will be open Friday, June 26, 2015, on the ACIP website. The registration deadline for Non-US citizens is September 30, 2015 and for US citizens registration closes October 7, 2015. Registration is not required for webcast viewing. As a reminder for non-US citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms are submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to help with any questions about the process.

Dr. Weinbaum recognized and welcomed the following visitors:

- Dr. Audry Mulumba, Medical Director, Expanded Program of Immunization (EPI), Democratic Republic of the Congo (DRC)
- Ms. Yolande Masembe, Epidemiologist, World Health Organization (WHO), DRC
- Dr. Antoinette Ba-Nguz, Africa Coordinator, Supporting National Independent Immunization and Vaccine Advisory Committees (SIVAC), a Bill and Melinda Gates Foundation funded initiative to strengthen national technical advisory committees for immunization

In addition, Dr. Weinbaum recognized and welcomed the following Liaison Representatives:

- Dr. Leonard Friedland, GlaxoSmithKline (GSK), Representing the Biotechnology Industry Organization (BIO) on Day 1
- Dr. Eddy Bresnitz, Merck, Representing BIO on Day 2
- Ms. Carol Hayes, Representing both the American College of Nurse Midwives (ACNM) and the American Nurses Association (ANA)

Dr. Weinbaum indicated that topics presented during ACIP meetings include open discussion with time reserved for public comment. She explained that time for public comment pertaining to topics on the agenda was scheduled following the afternoon sessions each day, and that time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before the vote. During this meeting, there were three public comment opportunities: 10:15 and 5:15 on Day 1 and at 12:45 PM on Day 2. People who planned to make public comments were instructed to visit the registration table at the rear of the auditorium where Ms. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide 3 pieces of information: Name, Organization if applicable, and any conflicts of interest (COI). Registration for public comment was solicited in advance of this meeting through the *Federal Register*. Given time constraints, each comment was limited to 3 minutes. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

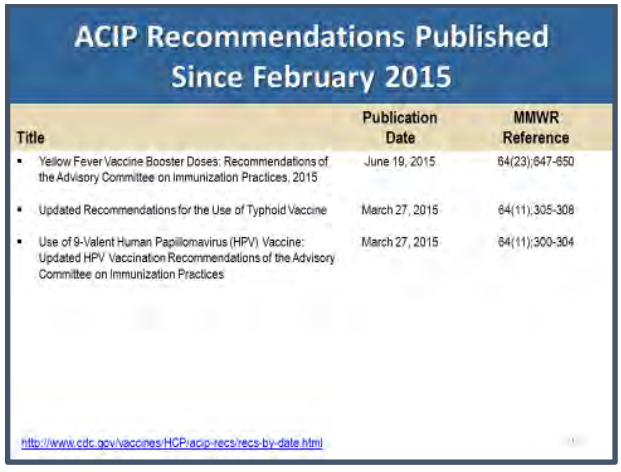
Regarding recommendations, ACIP uses a standard process to systematically collect and evaluate evidence behind each recommendation. More information about the Grading of Recommendation Assessment, Development and Evaluation (GRADE) process can be found on the ACIP website. Key factors for developing recommendations include the balance of benefits and harms, type or quality of evidence, values and preferences, and health economic analyses. The ACIP recommendation categories are:

- Category A: A recommendation that applies to all persons in an age- or risk-based group.
- Category B: A recommendation for individual clinical decision making.
- No recommendation for an unresolved issue.

Vaccine safety issues will continue to be presented at every ACIP meeting. During this meeting, these issues were included as part of specific topic presentations.

Regarding ACIP implications of the Affordable Care Act (ACA), ACIP recommendations become policy following approval by the CDC Director and publication in the *Morbidity and Mortality Weekly Report* (*MMWR*). The ACA was enacted in 2010, and requires insurance coverage for recommended immunizations without copays/deductibles when provided by an in-network provider. Health plans have one plan year from *MMWR* publication to implement recommendations according to CDC immunization schedules, including recommendations illustrated in the graphics and those described in footnotes.

During every meeting, an update is provided on the status of ACIP recommendations. There have been three ACIP publications since February 2015, which are reflected in the following table:



ACIP Recommendations Published Since February 2015

Title	Publication Date	MMWR Reference
▪ Yellow Fever Vaccine Booster Doses: Recommendations of the Advisory Committee on Immunization Practices, 2015	June 19, 2015	64(23);647-650
▪ Updated Recommendations for the Use of Typhoid Vaccine	March 27, 2015	64(11);305-308
▪ Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices	March 27, 2015	64(11);300-304

http://www.cdc.gov/vaccines/HCP/acip-recs/recs-by-date.html

Recommendations and immunization schedules can be downloaded from the ACIP website. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, revised, or retired.

Applications for ACIP membership are due no later than November 13, 2015 for the 4-year term beginning July 2016. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

E-mail: acip@cdc.gov Web homepage: http://www.cdc.gov/vaccines/acip/index.html

Nominations: http://www.cdc.gov/vaccines/acip/committee/req-nominate.html

A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submitted as e-mail attachments to Dr. Jean Clare Smith at jsmith2@cdc.gov

To summarize COI provisions applicable to the ACIP, as noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the proviso that he/she abstains on all votes related to the vaccines of that company. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

Before officially beginning the meeting, Dr. Temte called the roll to determine whether any ACIP members had conflicts of interest. The following conflicts of interest were declared:

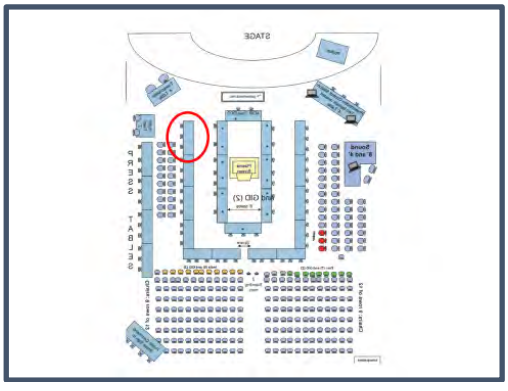
- ❑ Dr. Belongia: Receives research funding from Medimmune and has a conflict for influenza.
- ❑ The remainder of the ACIP members declared no conflicts.

Farewell to Parting ACIP Members

Jonathan Temte, MD, PhD
ACIP Chair

Dr. Temte shared some final comments, as his term as ACIP Chair would come to a close at the end of this meeting. He also recognized the other ACIP members who reached the end of their four-year terms and were rotating off of the committee, and presented each of them with a Certificate of Appreciation and a letter from Dr. Frieden, CDC's Director.

First, he showed the following seating chart and photograph, pointing out that for a number of years he and Drs. Bocchini and Campos-Outcalt sat together and that he was able to find a photograph from those days:



With Drs. Bocchini and Campos-Outcalt rotating off of the committee, Dr. Temte observed that ACIP was losing about 20 years' worth of experience.

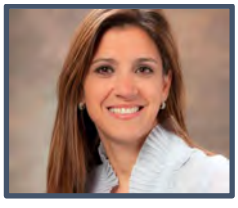
Joseph A. Bocchini, Jr. MD

Dr. Bocchini continues to practice Pediatric Infectious Disease at Louisiana State University (LSU) in Shreveport. He has a significant number of research interests, including special interest in vaccines; neonatal sepsis; and pharmacokinetics, toxicities, and interactions of antimicrobial agents in children. He has served as the Chair of the Human Papillomavirus (HPV) Work Group (WG) and the Yellow Fever/Japanese Encephalitis (YF/JE) WG. He served as the ACIP Liaison for American Academy of Pediatrics (AAP) Committee on Infectious

Diseases (COID). Two of his publications include *Immunizing adolescents: a selected review of recent literature and US recommendations* (2015) and *Improving vaccine risk/benefit communication with an immunization education package: a pilot study* (2002). Dr. Temte expressed appreciation for Dr. Bocchini's wisdom, knowledge, and enthusiasm throughout the last 11 years.

Doug Campos-Outcalt MD, MPA

Dr. Campos-Outcalt is currently a Senior Lecturer at the University of Arizona College of Medicine in Phoenix. He has considerable public health experience, including serving as a consultant to Papua New Guinea for two years. He also brings a lot of evidence-based science to the committee. He has served as the American Academy of Family Physicians (AAFP) liaison to the United States Preventive Services Task Force (USPSTF), as well as a member of the evidence-based Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG). He has served as the ACIP Chair for the H5N1 WG, and has been involved with the Meningococcal, Hepatitis, Evidence-Based Recommendations (EBR), and General Recommendations WGs. Some of his publications have included *Female-to-female transmission of syphilis: a case report* (2002), *Pedestrian fatalities by race/ethnicity in Arizona, 1990-1996* (2002), and *Catching up on the latest USPSTF recommendations* (2015). Though he is greatly appreciated and will be missed as a member, Dr. Campos-Outcalt plans to continue to help with GRADE support.



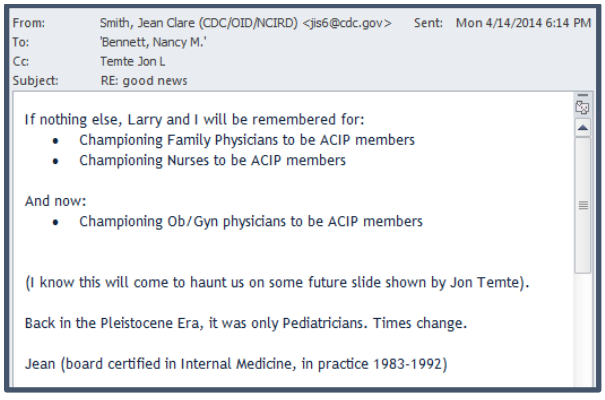
Marietta Vazquez, MD

Dr. Vazquez is Associate Professor of Pediatrics and Nursing at Yale School of Medicine in New Haven, Connecticut. Her research interests are in evaluating the effectiveness of pediatric vaccines, long-term outcomes of children infected with Lyme disease, and clinical epidemiology of newly diagnosed-respiratory infections in children. She has served as Chair of ACIP's General Recommendations and Rotavirus WGs, and as a member of the Meningococcal and Pertussis WGs. Some of her publications included *Effectiveness of varicella vaccine in children infected with HIV* (2010) and *Conservation of the Respiratory Syncytial Virus SH gene* (2000). Dr. Temte thanked Dr. Vazquez for her enthusiasm and wisdom on the committee.


Dan Hopfensperger

Dr. Temte also expressed gratitude to Dan Hopfensperger who retired on June 10, 2015 from his position as Wisconsin Immunization Program Director, Wisconsin Division of Health Services. He was the longest serving state immunization program manager at 38 years. He was instrumental in the development and maturation of the Wisconsin Immunization Registry (WIR).

Dr. Temte expressed gratitude to Dr. Jean Smith who he deemed the "grease and glue" in that she has been instrumental in lubricating the system, making it work, and holding it together behind the scenes. He shared the following email from Dr. Smith:



From: Smith, Jean Clare (CDC/OID/NCIRD) <jis6@cdc.gov> Sent: Mon 4/14/2014 6:14 PM
To: 'Bennett, Nancy M.'
Cc: Temte Jon L
Subject: RE: good news

If nothing else, Larry and I will be remembered for:

- Championing Family Physicians to be ACIP members
- Championing Nurses to be ACIP members

And now:

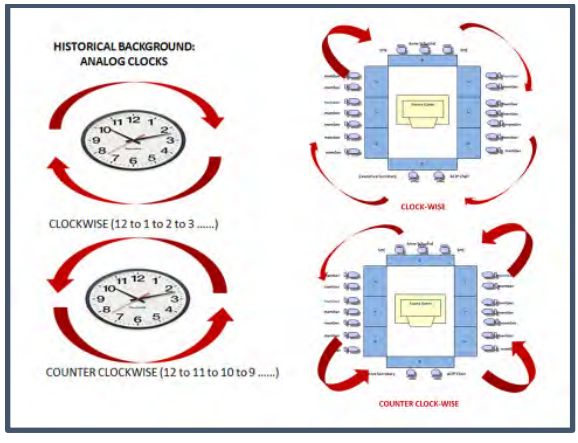
- Championing Ob/Gyn physicians to be ACIP members

(I know this will come to haunt us on some future slide shown by Jon Temte).

Back in the Pleistocene Era, it was only Pediatricians. Times change.

Jean (board certified in Internal Medicine, in practice 1983-1992)

He quipped that Dr. Smith always tries to make sure that ACIP does the right thing, and shared the following diagram that she created for the members to address the ongoing clockwise/ counterclockwise issue:



Dr. Temte shared the following quote to illustrate what he learned from ACIP:

> *"Poor fool[s], with all this sweated lore,*
> *[We] stand no wiser than we were before.*
> *Master and Doctor are our titles;*
> *For [51] years now, without repose,*
> *[We've] held [our] erudite recitals*
> *And [coaxed recommendations] by the nose.*
>
> *And round [we] go,*
> *on crooked ways or straight,*
> *And well [we] know that*
> *ignorance is our fate,*
> *And this [we] hate."*
>
> Faust
> Johann Wolfgang von Goethe, 1806

He pointed out that ACIP members find that no matter how much information they have, it is never enough. In 2010, ACIP adopted GRADE. At the time, he heard rumbling that GRADE would turn people into numbers. He played a clip from 42 years ago from Jacob Bronowski who was a Polish Mathematician. Dr. Temte said that he was going to play this clip during his first ACIP meeting as Chair, but Dr. Pickering would not let him. He quipped that this was to get back at Dr. Pickering in his absence:

> *"It's said that science will dehumanize people and turn them into numbers. That's false, tragically false. Look for yourself. This is the concentration camp and crematorium at Auschwitz. This is where people were turned into numbers. Into this pond were flushed the ashes of some four million people. And that was not done by gas. It was done by arrogance. It was done by dogma. It was done by ignorance. When people believe that they have absolute knowledge, with no test in reality, this is how they behave. This is what men do when they aspire to the knowledge of gods.*
>
> *Science is a very human form of knowledge. We are always at the brink of the known. We always feel forward for what is to be hoped. Every judgment in science stands on the edge of error and is personal. Science is a tribute to what we can know although we are fallible . . .*
>
> *We have to cure ourselves of the itch for absolute knowledge and power...*
>
> *We have to touch people."*
>
> Knowledge or Certainty
> The Ascent of Man, BBC
> Jacob Bronowski, 1973

Interestingly, Jacob Bronowski was the Director of the Salk Institute. ACIP deals with a lot of information, but also must put it into the context of the human element.

Dr. Temete shared the following lyrics from a Coldplay song and lines from a T.S. Eliot poem:

"I was just guessing at numbers and figures
Pulling your puzzles apart
Questions of science, science and progress
Do not speak as loud as my heart"

The Scientist
A Rush of Blood to the Head
Coldplay, 2002

"Where is the Life
we have lost in living?
Where is the wisdom
we have lost in knowledge?
Where is the knowledge
we have lost in information?"

T. S. Eliot
The Rock, 1934

In an effort to put this all together, Dr. Temte quoted the following from the Grinch in Dr. Seuss's "How the Grinch Stole Christmas" from 1957 with a little embellishment:

"[They] puzzled and puzzled till [their] puzzler was sore.
Then [ACIP] thought of something [they] hadn't before.
Maybe [recommendations], [they] thought…
don't come from a score.
Maybe recommendations, perhaps…
[mean] a little bit more!"

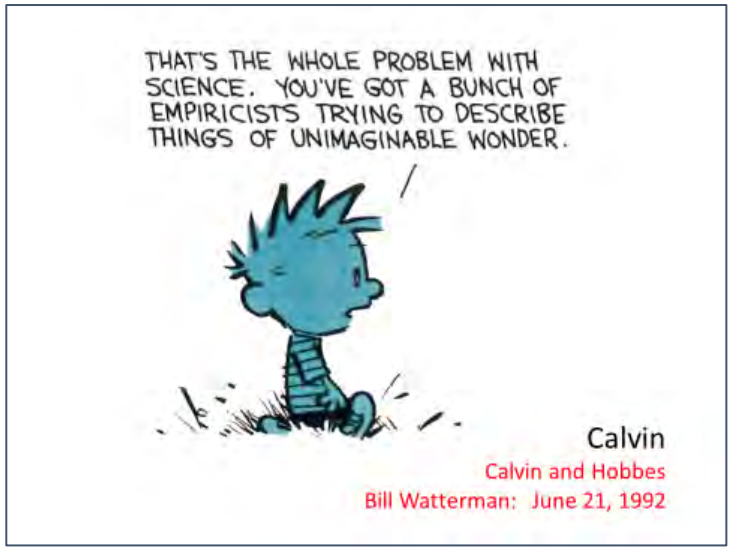
The Grinch
How the Grinch Stole Christmas
Dr. Seuss. Random House;
November 24, 1957

With the GRADE process, ACIP gathers information. But after the information is collected, it is filtered through topics such as cost-effectiveness, balances of harms and benefits, and values and preferences. Dr. Temte shared the following excerpt from a public comment:

"We worry about cost-effectiveness.
Is this cost-effective?
Is Ethan cost-effective?...
I say to you one baby, one child,
one teen is too many,
especially when it comes to being yours."

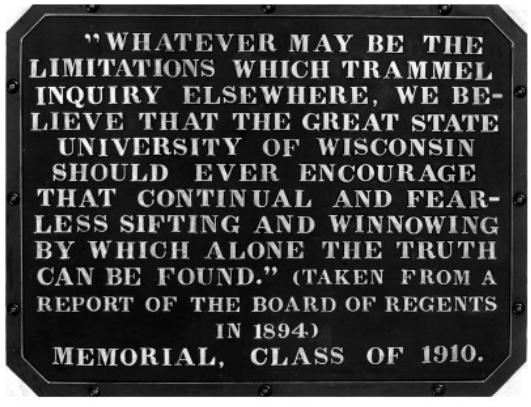
Frankie Milley
Founder/National Director, Meningitis Angels
Public Comment, ACIP October 23/24, 2013

This reminded Dr. Temte of a conversation with Dr. Mike Marcy who said, “When it comes to hard recommendations, what would you do for your child?” He then shared the following Calvin and Hobbes to illustrate the problem with science:



Dr. Temte pointed out that during this meeting’s meningococcal session, there would be an unprecedented number of public comments. As of last count, approximately 40 letters had been received on this topic. This included a letter with approximately 1200 co-signatures and a petition with 601 co-signatures. He pointed out that this reflected ACIP’s position as a federal advisory committee. Through the GRADE process, it is ACIP’s duty not only to review all of the evidence, but also to consider other issues such as values and preferences. With that in mind, Dr. Temte emphasized that public comments must be taken into consideration.

As a child, Dr. Temte said he first heard about “continual and fearless sifting and winnowing” from his father, who was a University of Wisconsin Professor as well. He emphasized that for ACIP, it is important to encourage “continual and fearless sifting and winnowing by which alone the truth can be found”:



Plaque at the entrance to Bascom Hall – University of Wisconsin

In closing, Dr. Temte reminded everyone that the inscription on the ACIP bell reads, “May The ACIP Recommendations Always Ring Clearly.” The bell was gifted to ACIP by Dr. Samuel Katz in 1993:

Farewell to Dr. Temte

Anne Schuchat, MD
Cindy Weinbaum, MD
Jean Clare Smith, MD, MPH

Dr. Schuchat thanked Dr. Temte for his incredible service, as well as the incredible material of his life that she featured in her farewell slideshow. Dr. Temte began his education in Iowa studying zoology and went on to earn an MD and PhD, featuring families throughout his career. The subject of Dr. Temte’s PhD dissertation was harbor seals and fertile periodicity:

Betty and pup Lucille
Madison Wisconsin 1983
Subject of Dr. Temte’s PhD Dissertation

Dr. Temte and recovering abandoned harbor seal pup, Oregon coast

The idea of the circle of life became a theme in Dr. Temte's career. He continued in family medicine in Wisconsin, and continued to carry out the full spectrum of family medicine until he dropped obstetrics in 2000 when his own family made him realize that delivering other people's babies was a little "too scary."

Dr. Temte's attraction to vaccines dates back to the first Rubella Elimination meeting he attended at CDC on October 29, 2004. He has continued that interest in the international arena. In 2013, Dr. Li Li, the Director of the National Immunization Program in China, spent an exchange with CDC in Atlanta and also visited Dr. Temte to learn about implementation and use of the Wisconsin Immunization Registry. Dr. Li Li invited Dr. Temte to China where he presented a GRADE seminar to China's ACIP equivalent. A favorite memory was a special "five-face" meal Dr. Temte enjoyed while there.

Dr. Temte's last three publications literally "span the waterfront" from the Pacific harbor seal, Betty, the oldest seal on record to give birth at 42, to his entry into the climate change debates and his passion for vaccine acceptance and misconceptions:

- Temte JL, Flynn E. Phenomenal advanced age of pupping in a captive Pacificharbor seal (Phoca vitulina richardsi). *Zoo Biology*. 2015 [accepted].

- Barrett B, Charles JW, Temte JL. Climate change, human health, and epidemiological transition. *Prev Med*. 2015;70:69-75.

- Epling JW, Savoy ML, Temte JL, Schoof BK, Campos-Outcalt D. When vaccine misconceptions jeopardize public health. *J Fam Pract*. 2014;63(12):E1-7.

Many people leave ACIP and experience a post-partum depression of sorts. However, Dr. Temte's fishing buddies have offered to help him ease the pain and with the great family that he enjoys, it is unlikely that Dr. Temte will suffer post-partum depression as he leaves ACIP. While ACIP is busy with the October 2015 meeting, he will be training for his next 5K.

In closing, Dr. Schuchat shared the following poem from the CDC/ACIP family in appreciation for Dr. Temte's service as ACIP Chair:

Farewell to Dr. Temte
Whose tank is never empty
As Chair he's now quite comfy
No risk of Humpty Dumpty
In case you missed the memo
Let me provide a demo
Pronunciation T-E-M-T-E
No relative of K-E-M-P-E see
He kept the schedules calm
'Til pneumo dropped a bomb
We'll need an extra meeting
The conference lines were bleeping
His temperament so staid
He's passionate for GRADE
His welcomes always warm
They'll melt a Southern storm
Of course, we're going to miss him
So go ahead and kiss him
Unless that is a no, no
We better check with MASO

Dr. Schuchat concluded that personally, it had been wonderful working with Dr. Temte. For those attending an ACIP meeting for the first time, she explained that this is not how meetings usually begin. However, Dr. Temte put his own personal touch on ACIP's deliberative values and the GRADE process.

Dr. Weinbaum presented Dr. Temte with a note from Dr. Larry Pickering in appreciation of their long work together, a letter from Dr. Frieden, and a Certificate of Appreciation.

Dr. Smith indicated that when she was in internal medicine practice in Boston for 10 years before coming to the CDC, she went to an antiquarian book fare one day where she found a certificate dated 1792:

> "To Dr. Welch: Please to inoculate two children of McGower on account of the town of Boston agreeable to the vote for that purpose."
>
> W. Smith
> Overseer of the Poor

This was an instruction to Dr. Welch in Boston, Massachusetts, Overseer of the Poor, to administer smallpox variolation to two children in August 1792. Dr. Smith noted that the certification was in immaculate condition and cost her $1.00. She also indicated that Dr. Jose Romero provided a chapter called "Early Efforts of Controlled Variolation Vaccination and Isolation and Quarantine" from a book titled "Smallpox and Its Eradication."

Dr. Smith noted that in the 1980s, the predecessor of the National Immunization Program (NIP) created several Dr. Seuss posters and adapted language from his children's books to contain immunization messages. She presented Dr. Temte with a framed poster with language from "If I Ran the Zoo."

Meningococcal Vaccines

Introduction

Lorry Rubin, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

Dr. Rubin reminded everyone that two serogroup B Meningococcal (MenB) vaccines are licensed in the United States (US) and approved for use in persons 10 through 25 years of age:

- MenB-FHbp (Trumenba®, Pfizer) licensed on October 29, 2014
- MenB-4C (Bexsero®, Novartis) licensed on January 23, 2015

Both vaccines were licensed under an accelerated pathway. MenB vaccines are distinct from MenACWY conjugate vaccines because protection is based upon developing immunity to bacterial proteins rather than to capsular polysaccharides. Recent presentations to ACIP regarding MenB vaccines have included the following:

- February and June 2014
  - → Epidemiology of meningococcal disease outbreaks and outbreaks of serogroup B meningococcal disease on university campuses
  - → Interim guidance for the use of a MenB vaccine under a CDC-sponsored expanded access investigational new drug (IND)

- October 2014
  - → Safety and immunogenicity for MenB-FHbp and MenB-4C
  - → Epidemiology of serogroup B meningococcal disease in the US
  - → Considerations for use of MenB vaccines in the US

- February 2015
  - → Considerations for use of MenB vaccines in persons at increased risk, with discussion and a vote

The ACIP recommendation for use of MenB vaccine in persons at increased risk for meningococcal disease, which is a Category A recommendation, is as follows:

> A serogroup B meningococcal (MenB) vaccine series should be administered to persons aged ≥10 years at increased risk for meningococcal disease. (Category A) This includes:
>
> - Persons with persistent complement component deficiencies[1]
> - Persons with anatomic or functional asplenia[2]
> - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
> - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)
[2]Including sickle cell disease

The activities since the last ACIP meeting resulted in a Policy Note regarding the use of MenB vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease that was published on June 12, 2015. The WG has been reviewing the available safety, immunogenicity, and epidemiological data and discussing policy options for broader use of MenB vaccines in adolescents and college students. Policy options for broader use of MenB vaccines concern administration of a MenB vaccine series at 11 to 12 years of age with an anticipated booster at 16 years of age. Also under consideration is administration of the vaccine at 16 years of age, 18 years of age, or among college students only. The recommendation options are:

- Category A (for all persons in an age- or risk-factor-based group)
- Category B (for individual clinical decision making)
- No recommendation

Presentations during this session include the following:

- GRADE: Evidence for use of MenB vaccines in adolescents and college students
- Considerations for routine use of MenB vaccines in adolescents
- Public comment
- Proposed policy option language and vote
- VFC vote

MenB vaccines certainly are challenging for ACIP. Of course, the goal is to prevent the largest proportion of cases of meningococcal disease possible. The recently licensed MenB vaccines are an important step forward. However, data for making policy decisions for vaccine use are not complete in terms of effectiveness, strain coverage in the US, duration of protection, effect on carriage and herd immunity, and expanded safety. In addition, the burden of serogroup B meningococcal disease in adolescents and young adults is currently low.

GRADE: Evidence for Use of MenB Vaccine in Adolescents and College Students

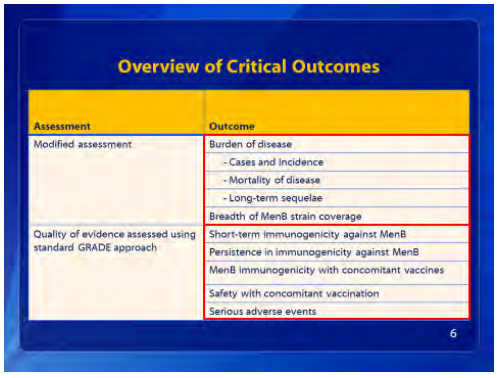
Temitope A. Folaranmi MD, MPH, MPP
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Folaranmi presented the GRADE evaluation for use of MenB vaccines in adolescents and young adults, including college students. He reviewed the study questions for GRADE, the modified assessment for the quality of disease burden, the breadth of MenB strain coverage, and the GRADE assessment for evidence of outcomes. The study question addressed was:

> "Should MenB vaccines be routinely administered to all adolescents and young adults (including college students)?"

There are two MenB vaccines licensed in the US. MenB-4C (Bexsero®) is a multi-component vaccine manufactured by Novartis, now GSK, and is a two-dose series. MenB-FHbp (Trumenba®) is a bivalent recombinant lipoprotein vaccine manufactured by Pfizer and is a three-dose series.

After selecting the study question, the next step in the GRADE process was to select outcomes that the WG believed to be important and critical to answer this question. This table shows outcomes that were ranked critical for the study questions. The first two outcomes were rated using a modified assessment since they are surveillance data, and the last five outcomes were assessed using GRADE:



Regarding the quality of meningococcal disease burden data, since the incidence of meningococcal disease has reached historic lows in the US in recent years, the WG felt that rating the quality of disease burden data would be a key component for this assessment. However, because these data were from surveillance and no intervention was tested, the WG could not evaluate the data in the GRADE format. Instead, they assessed the disease burden data for accuracy, applicability, and representativeness. The US meningococcal incidence data come from two sources: the Active Bacterial Core surveillance (ABCs) and the National Notifiable Disease Surveillance System (NNDSS). ABCs is an active surveillance system of 10 US sites that is used to estimate incidence of meningococcal disease in the US. It is limited to only culture-confirmed cases, and therefore, an 18% correction factor is added to account for polymerase chain reaction (PCR)-confirmed cases. ABCs provides data on a variety of factors, including historical trend, risk factors, vaccination, and molecular data.

However, due to the low case counts in ABCs in recent years, an integrated approach for meningococcal disease surveillance data is being used. This approach includes NNDSS, a passive surveillance system that captures information on all cases, including cases confirmed by PCR only and those with clinically compatible illness. Historically, serogroup and case-outcome information has been limited, so these have been supplemented by ABCs and health departments since 2005. A capture-recapture analysis that was performed in Maine from 2001 to 2006 demonstrated high sensitivity of state surveillance data when compared to hospital discharge records. Accuracy of disease burden data was improved when using an integrated approach to surveillance. Both ABCs and NNDSS surveillance systems were determined to be applicable, as they both capture meningococcal disease incidence in adolescents and young adults. Although ABCs is limited to 10 sites and may not be representative of the national meningococcal disease incidence, NNDSS is reported by all states and is considered representative of national meningococcal disease incidence.

To complete the assessment of the burden of disease data quality, the WG reviewed morbidity and mortality data, using mortality data collected from ABCs and NNDSS, and long-term sequelae data that were captured in published manuscripts. Estimates of case-fatality rates and long-term sequelae varied depending upon the source, and ranged from 2% to 10% for case-fatality rate and 5% to 50%[1] for long-term sequelae. ABCs and NNDSS capture all meningococcal data among adolescents. However, serogroup-specific information may not

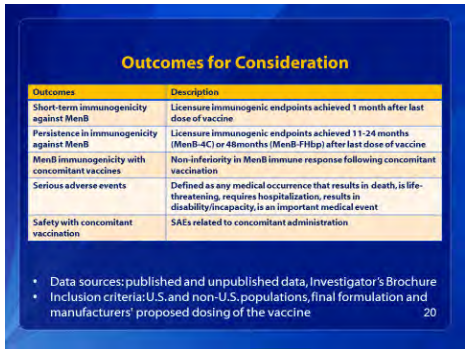
always be available. Published reports of long-term sequelae from all-cause bacterial meningitis are often hospital-based studies with small sample sizes, and have limited information on age and serogroups. Based on the evaluation of meningococcal disease incidence, mortality, and morbidity data, minor limitations were found in terms of representativeness, accuracy, and applicability. However, the WG did not feel that this significantly affected the quality of its burden of disease estimates [[1]Bedford et al., BMJ 2001, 323: 533-7;Chandran et al., PIDJ 2011, 30:3-6.; Erickson and De Wals. CID 1998, 26:1159-64; Kaplan et al., Pediatrics 2006, 118(4):e979-84].

In terms of the modified assessment of strain coverage, vaccine targets for MenB vaccines are antigenically diverse and are variably expressed among circulating MenB strains in the US. However, there are no data demonstrating bactericidal activity against all circulating invasive MenB strains in the US. For the Pfizer vaccine, MenB-FHbp, FHbp sequence analysis and surface expression by flow cytometry was performed for an epidemiologically representative collection of 1263 MenB strains, of which 432 were US isolates. FHbp was expressed in about 95% of the serogroup B isolates tested. The analysis demonstrated durability between subfamilies, as well as surface expression of FHbp. In a subset of isolates for which bactericidal activity was assessed, isolates with moderate or high level of expression of FHbp was predictive of bactericidal activities; whereas, there was a lower correlation among isolates with low expression of FHbp [Jiang et al., Vaccine 28 (2010) 6086-6093].

For the Novartis vaccine, MenB-4C, the Meningococcal Antigen Typing System (MATS) was used to estimate coverage. MATS is a sandwich enzyme-linked immunosorbent assay (ELISA) that measures cross-reactivity with vaccine antigens, as well as a level of expression of each antigen to predict bactericidal activity against a broad number of strains. In order to assess the immunogenicity of each antigen, four of the primary strains were selected based on having cross-reactivity with 1 vaccine antigen while having limited cross-reactivity with other vaccine antigens, and thus were not representative of circulating strains in the US. MATS was previously bridged to serum bactericidal activity using human complement (hSBA) in a subset of antigenically diverse strains and was found to be greater than 80% predictive of bactericidal activity when one antigen was expressed above a certain threshold, and greater than 90% when at least two antigens were expressed above a certain threshold. Based on the analysis of over 400 US isolates, MenB-4C is estimated to cover 91% of circulating strains in the US [Donnelly et al., PNAS (2010) vol. 107, no. 45. Based on a representative strain panel of invasive MenB isolates from 2000-2008 selected by US CDC (adjusted with respect to strains from Oregon)].

In summary, true breadth of coverage of endemic MenB disease has only been estimated for these two vaccines. The manufacturers have used two different methods to assess the breadth of coverage for their vaccines, and secondary studies to evaluate immunogenicity against additional strains are pending.

These are the five outcomes for consideration in the GRADE analysis:

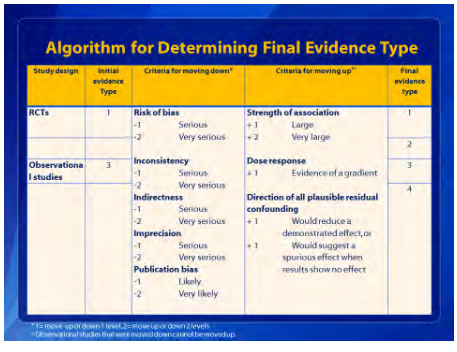


The data sources included published and unpublished data, as well as information from the investigator's brochure. Studies conducted in US and non-US populations were included as long as the final formulation and the manufacturer's proposed dosing for the vaccine was used. Due to the low incidence of serogroup B meningococcal disease, an efficacy trial using clinical endpoints was impractical. Therefore, vaccine efficacy estimates were based on the demonstrations of a functional immune response in recipients against a small number of serogroup B strains. In studies supporting US licensure, immunogenicity was assessed by the proportion of subjects who achieved a greater than or equal to four-fold increase in hSBA titers for each of the strains tested, and the proportion of the subjects who achieved a titer greater than or equal to the lower limit of quantitation of the assay for all strains, referred to as the composite response. The lower limit of quantitation was defined as the lowest amount of antibody in a sample that can be reliably quantified. Although the licensure endpoints are the same, data from MenB-FHbp and MenB-4C are not directly comparable because, for example, the persons were each tested against different serogroup B strains.

As a reminder, the criteria used for GRADE analysis are as follows:

- ❑ Risk of bias (methodological limitations)
- ❑ Inconsistency
- ❑ Indirectness
- ❑ Imprecision
- ❑ Other considerations (publication bias, strength of association, dose gradient)

The following algorithm is used to determine the final evidence type for each outcome:



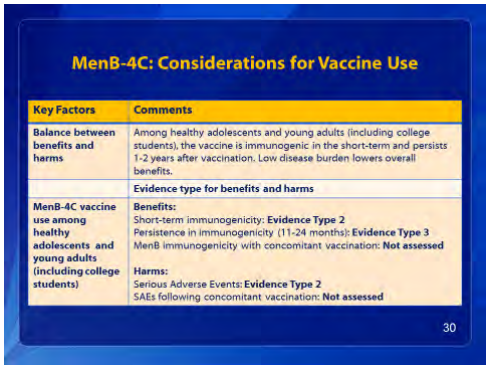
Randomized controlled trials (RCTs) begin as an evidence type of 1, and observational studies begin as 3. The five criteria are assessed to determine whether the evidence type is moved up or down.

In terms of the evaluation of these outcomes for Bexsero®, MenB-4C, there were five studies including one non-controlled, open-label study and four RCTs. The majority of the studies assessed multiple outcomes. Four of the studies have been published. However, the WG also assessed unpublished data where available. In addition, the WG reviewed severe adverse events (SAE) for post-vaccination data. No studies assessing safety and immunogenicity with concomitant vaccine have been completed.

For evidence of benefits, short-term immunogenicity after a two-dose series ranged from 63% to 94%, depending upon the study. Persistence was measured 11 to 24 months after vaccination with the two-dose series and ranged from 66% to 94%, depending upon the study. For evidence of harms based on SAEs, of all the studies assessed, a total of 3140 participants received at least one dose of the vaccine. Among the vaccine subjects, 67 SAEs were reported. In most cases, the SAE rate was similar between the MenB vaccine group and other groups within each study. Five SAEs were considered related to MenB vaccines, and no concerning pattern was observed among these SAEs. Two deaths unrelated to the vaccine were reported in one of the studies. Review of SAE surveillance data from vaccination campaigns conducted in Princeton, Santa Barbara, and Quebec showed that of the 59,000 participants who received at least one dose of the vaccines, 60 SAEs were reported and three SAEs were considered related to the vaccine. All three SAEs resolved over time. One death was reported, but was determined to be unrelated to the vaccine.

For risk of bias, the WG downgraded the persistence in immunogenicity outcome by 1 due to potential selection bias and unplanned sample size determination. For consistency, the WG downgraded the short-term immunogenicity outcome by 1 due to high heterogeneity between studies. For indirectness, the WG downgraded short-term immunogenicity and persistent immunogenicity outcomes by 1 each for indirect assessment of vaccine efficacy. For imprecision, the WG downgraded SAE outcomes by 1 because the confidence interval around the effect estimates includes effect and non-effect. The short-term immunogenicity outcome was upgraded by 1 for the strong strength of association. The overall evidence type is 2 for short-term immunogenicity, 3 for persistence immunogenicity, and 2 for the two SAEs. Safety and immunogenicity following concomitant vaccination was not assessed.

The following table summarizes the balance between benefits and harms, as well as the evidence type:



MenB-4C: Considerations for Vaccine Use

Key Factors	Comments
Balance between benefits and harms	Among healthy adolescents and young adults (including college students), the vaccine is immunogenic in the short-term and persists 1-2 years after vaccination. Low disease burden lowers overall benefits.
	Evidence type for benefits and harms
MenB-4C vaccine use among healthy adolescents and young adults (including college students)	**Benefits:** Short-term immunogenicity: **Evidence Type 2** Persistence in immunogenicity (11-24 months): **Evidence Type 3** MenB immunogenicity with concomitant vaccination: **Not assessed** **Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Not assessed**

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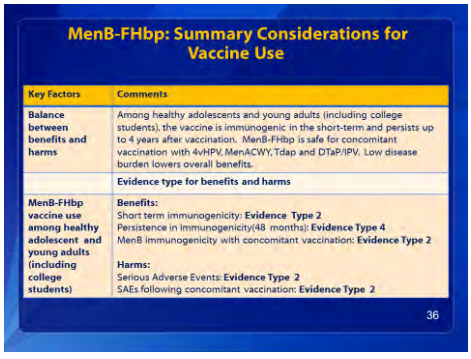
Regarding the evidence type of Trumenba®, MenB-FHbp, there were seven studies including two non-controlled studies and five randomized-controlled studies. The majority of studies also assessed multiple outcomes. Three of the studies have been published. Non-published data were also reviewed from these studies. For evidence of benefits, short-term immunogenicity measured one month after a three-dose series ranged from 80% to 81%, depending upon the study. Based on non-inferiority criteria, no immunologic interference was observed for MenACWY, Tdap, TdaP/IPV, or HPV types 6,11,16. Persistence was measured at the 48th month after vaccination with the three-dose series and demonstrated protective titers against three of the four primary strains in more than 50% of the subjects.

For evidence of harms, a total of 11,338 participants received at least one dose. SAEs were reported among subjects. In most cases, SAE rates were similar between vaccine groups and other groups in each study. Seven SAEs were considered related to MenB-FHbp. No concerning pattern was observed among these events. One death unrelated to the vaccine was reported. For risk of bias, the WG downgraded persistence in immunogenicity outcome by 1 due to its very small sample size. For indirectness, the WG downgraded short-term immunogenicity, persistence in immunogenicity, and MenB immunogenicity with concomitant vaccination each by 1 each due to indirect use of correlate of immunogenic endpoints to measure efficacy. For imprecision, the WG downgraded both SAE outcomes by 1 each because the confidence interval around the effect estimate includes both effect and non-effect. Short-term immunogenicity was upgraded by 1 due to the strong strength of association. The overall evidence type turned out to be 2 for short-term immunogenicity, 4 for persistence in immunogenicity, 2 for MenB immunogenicity with concomitant vaccination, and 2 for both SAEs.

The following table summarizes the balance between benefits and harms, as well as the evidence type:



MenB-FHbp: Summary Considerations for Vaccine Use

Key Factors	Comments
Balance between benefits and harms	Among healthy adolescents and young adults (including college students), the vaccine is immunogenic in the short-term and persists up to 4 years after vaccination. MenB-FHbp is safe for concomitant vaccination with 4vHPV, MenACWY, Tdap and DTaP/IPV. Low disease burden lowers overall benefits.
	Evidence type for benefits and harms
MenB-FHbp vaccine use among healthy adolescent and young adults (including college students)	**Benefits:** Short term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity(48 months): **Evidence Type 4** MenB immunogenicity with concomitant vaccination: **Evidence Type 2** **Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Evidence Type 2**

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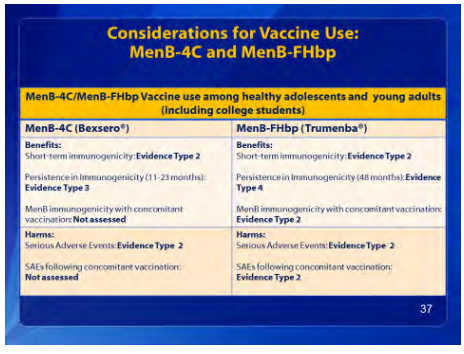
The following table summarizes the evidence type for both vaccines graded:



Considerations for Vaccine Use: MenB-4C and MenB-FHbp

MenB-4C/MenB-FHbp Vaccine use among healthy adolescents and young adults (including college students)

MenB-4C (Bexsero®)	MenB-FHbp (Trumenba®)
Benefits: Short-term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity (11-23 months): **Evidence Type 3** MenB immunogenicity with concomitant vaccination: **Not assessed**	**Benefits:** Short-term immunogenicity: **Evidence Type 2** Persistence in Immunogenicity (48 months): **Evidence Type 4** MenB immunogenicity with concomitant vaccination: **Evidence Type 2**
Harms: Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Not assessed**	**Harms:** Serious Adverse Events: **Evidence Type 2** SAEs following concomitant vaccination: **Evidence Type 2**

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Considerations for Routine Use of MenB Vaccines in Adolescents

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. MacNeil presented a summary of the WG's considerations for use of serogroup B meningococcal vaccines in adolescents. She summarized the data reviewed by the WG, and presented the policy options and the WG's considerations for use of MenB vaccines in adolescents and the proposed policy option language for this session's vote.
In the US, the incidence of meningococcal disease is currently at an historic low. In 2013, a total of 564 cases of meningococcal disease were reported. Declines in incidence have been observed for all of the serogroups, including serogroup B, which is not included in the meningococcal conjugate vaccines. In addition, despite steady increases in coverage with conjugate vaccine among adolescents, much of the decline in incidence occurred prior to high levels of coverage in adolescents. In 2013, coverage with one or more doses of conjugate vaccine was estimated to be 77% among those 13 through 17 years of age, but varied from 40% to 94% by state. Two-dose series completion was estimated to be less than 30%. As the current adolescent program has become more established, the first impact of the program on rates of serogroup C/Y/W meningococcal disease has been observed. The combined incidence of C/Y/W has decreased by 80% from 2004 to 2005 to 2012 to 2013 among those 11 through 19 years of age. The same decline in incidence has not been observed among persons in age groups that are not routinely receiving conjugate vaccines, including infants less than one year of age and persons 20 years of age and older. Incidence in adolescents and young adults is similar for serogroup B and serogroups C and Y combined. The remaining burden of serogroups C and Y disease in this age group highlights the need for additional efforts to reinforce the importance of the second dose of the conjugate vaccine in the current adolescent program.

In terms of annual cases, deaths, and cases that result in long-term sequelae from serogroup B and serogroups C and Y meningococcal disease, it is estimated that in recent years, serogroup B has caused approximately 55 to 65 cases annually in those 11 through 24 years of age. Approximately 80% of those cases occurred in older adolescents and young adults 16 through 24 years of age. In the US, approximately 61% of those 18 through 23 years of age enroll in college. Information on college attendance for meningococcal cases is collected through ABCs, but is not collected through NNDSS. In recent years, approximately 40% of serogroup B cases among those 18 through 23 years of age reported to ABCs attended college. That proportion can be applied to serogroup B cases reported to NNDSS in this age group to estimate the number of meningococcal cases occurring in college students nationwide.

From 2009 through 2013, there were an estimated 14 cases of serogroup B meningococcal disease in college students annually, with two deaths in this age group. The incidence of serogroup B meningococcal disease among college students was similar to the incidence among all 18 through 23 year olds and to non-college students. Although a similar risk is estimated for serogroup B meningococcal disease in college students and non-college students in this age group, seven clusters or outbreaks of serogroup B meningococcal disease have been reported to CDC from university campuses since 2009, including two since the beginning of 2015. As a result of these outbreaks, the number of surveillance sites reporting information on college attendance was expanded in order to better track the burden of disease in this group.

Beginning in 2013, enhanced surveillance was established for cases of meningococcal disease among college students in an area which covers approximately 60% of the US population. In 2013 and 2014, approximately 65% of serogroup B cases among 18 through 23 year olds in these sites have been reported in college students, with two deaths reported each year. However, even with the enhanced surveillance sites collecting additional information on cases occurring in this population, there are years during which more cases and deaths occur. For example, in 2014 three deaths from serogroup B meningococcal disease in college students were reported to CDC, one of which occurred outside of the enhanced surveillance area.

To summarize, the US is currently experiencing a historic low in meningococcal disease incidence. The incidence of disease has declined for all meningococcal serogroups, including serogroup B, which is not included in the conjugate vaccines. For the last several years, the US has remained at a stable low in disease incidence, with approximately 55 to 65 cases of serogroup B meningococcal disease reported in adolescents and young adults each year. The majority of serogroup B cases in adolescents occur in older adolescents and young adults 16 through 24 years of age. Approximately 40% to 70% of serogroup B cases in 18 through 23 year olds occur in college students. However, incidence in both college and non-college students is similar.

Regarding the immunogenicity data for the MenB vaccines, there are two serogroup B meningococcal vaccines licensed in the US for use in persons 10 through 25 years of age as previously noted. MenB-FHbp contains both subfamilies of FHbp and is administered as a three-dose series. MenB-FHbp was licensed by the Food and Drug Administration (FDA) in October 2014. MenB-4C contains four components and is administered as a two-dose series. MenB-4C was licensed for use in the US by FDA in January 2015, and is also licensed in a number of other countries for use in persons two months of age and older.

As reported by Dr. Folaranmi, vaccine efficacy was estimated from serum bactericidal antibodies against a small number of serogroup B strains. In studies supporting US licensure, immunogenicity was assessed by both the proportion of subjects who achieved a greater than or equal to four-fold increase in hSBA titer for each of the strains tested and a proportion of subjects who achieved a titer greater than or equal to the lower limit of quantitation of the assay for all strains, or the composite response. Although licensure endpoints are the same, data from MenB-FHbp and MenB-4C are not directly comparable. The complete immunogenicity and safety data that supported licensure of MenB-FHbp was presented by Pfizer during the October 2014 ACIP meeting. To summarize, MenB-FHbp has a demonstrated immune response in the general adolescent population. Of the subjects, 84% had a composite hSBA response to four strains after three doses, and 50% had a composite response after two doses.

Data on concomitant administration of MenB-FHbp and the other adolescent vaccines is reassuring. No immunologic interference was observed for serogroup B or vaccine antigens including HPV types 6/11/16, MenACWY, TdaP, and IPV antigens. For HPV type 18, non-inferiority criteria were not met for the geometric mean titer (GMT) ratio at one month after the third quadrivalent HPV vaccination. However, 99% of subjects achieved seroconversion for all four HPV antigens. Antibody persistence data through 48 months post-dose 3 from MenB-FHbp was recently presented to the WG. The proportion of subjects with hSBA titers $\geq$ 1:4 peaks at one month following the third dose for all four strains tested. For Strains A22 and B24, which represent more prevalent FHbp subvarients in the US, the proportion of subjects with protective titers falls quickly to approximately 60% by six months following the third dose, but then remains stable through 48 months post dose 3.

Immunogenicity and safety data for MenB-4C were also presented during the October 2014 ACIP meeting. Immunogenicity data from the three main trials conducted in Canada-Australia, the UK, and Chile were used to assess the effectiveness of MenB-4C. Of the subjects, 63% to 94% had a composite hSBA response to three strains after two doses. The immunogenicity data from the Canadian-Australian study conducted in adolescents 11 through 17 years of age was included in the package insert because the hSBA responses generated by the study participants were more likely representative of the responses in the US population as compared to the Chilean study, which also enrolled adolescents 11 through 17 years of age. The UK study, conducted in young adults between the ages of 18 and 24 years of age, was also included in the package insert to provide data on young adults 18 through 25 years of age. Antibody persistence following two doses of MenB-4C has been examined in two of these studies. Of subjects in a study among UK university students, 66% maintained a composite hSBA response to the three strains 11 months post-dose 2. Among Chilean adolescents, 77% to 94% maintained an hSBA response $\geq$ 1:4 18 to 24 months post-dose 2. However, pre-vaccination hSBA titers were also higher in the Chilean adolescents compared to what is expected for the US population. No concomitant administration data are available for MenB-4C.

Recently, preliminary results from a seroprevalence survey conducted at Princeton University by Nicole Basta were also shared with the WG. As a reminder, between March 2013 and March 2014, nine cases of serogroup B meningococcal disease occurred in persons linked to Princeton University, including one death. Laboratory-typing results were identical for the A isolates that were available, and all were ST-409, which is uncommonly seen in the US. A mass-vaccination campaign using MenB-4C was held in December 2013, and a second-dose campaign was held in February 2014. Smaller catch-up campaigns were held following each mass clinic. Overall, coverage among undergraduates by the end of the vaccination campaigns was 98% for the first dose and 93% for the second dose. A cross-sectional seroprevalence survey was launched in April 2014, and 607 participants were enrolled. Focusing on the largest group of subjects who received both doses during the mass clinics in December and February, approximately 66% of subjects had an hSBA titer $\geq$ 1:4 against the outbreak strain in April 2014, two months after the second dose of MenB-4C. From the original 607 participants, a subset of 245 samples were selected to assess immune response against one of the vaccine strains. Nearly all subjects who received two doses of MenB-4C had hSBA titers $\geq$ 1:4 against the 5/99, or NadA, vaccine reference strain. In addition, GMTs were much higher for the vaccine reference strain compared to the outbreak strain [Basta et al. Immunological Response following the Introduction of a Novel Meningococcal B Vaccine during an Outbreak at a University in 2013-2014. In preparation].

To summarize the WG's interpretation of the available immunogenicity data, immunogenicity studies predict efficacy of the MenB vaccine in the short-term. However, there is evidence of waning antibody levels within six months post-dose 3 for MenB-FHbp, and there appears to be modest antibody waning observed through 24 months post-dose 2 for MenB-4C. In addition, in the Princeton study, the proportion of responders to the outbreak strain appeared to be lower than to the vaccine reference strain, which highlights that the proportion of vaccinees who develop bactericidal antibodies protective against each outbreak or circulating strain may differ.

Regarding safety data for the MenB vaccines from clinical trials, post-vaccination local and systemic complaints are common. The most frequently reported solicited adverse events (AEs) were pain at the injection site, fever, headache, fatigue, myalgia, and arthralgia. Reactions were typically self-limited and resolved within three to seven days. The MenB vaccines were more reactogenic than other routine vaccines for adolescents based on the proportion of subjects who report the most severe category of local and systemic adverse events. Rates of SAEs reported in the clinical trials were similar between vaccine recipients and controls.

There is some limited experience with the safety of MenB vaccines outside of clinical trials. Most of the experience is with MenB-4C, which was administered to approximately 17,000 persons vaccinated under an expanded access IND program for outbreak response at two US universities and over 40,000 persons vaccinated in a regional public health program in Quebec. No concerning patterns among the AEs were observed following any of these vaccination programs. For MenB-FHbp, safety data were collected during one of the recent outbreak response; however, those data are not yet available.

The WG also reviewed data from animal models that showed auto-antibodies in some animals following MenB vaccination[1-3], which raises theoretical concerns about the development of auto-immune disorders. FDA reviewed the clinical data and did not observe differences in rates of auto-immune disorders between vaccine recipients and controls. The data do not suggest a higher incidence of autoimmune conditions following vaccination than what is observed in the general population. Theoretically, onset of auto-immune symptoms could be delayed well beyond vaccination. Post-licensure safety surveillance will be conducted to detect any potential safety signals. However, this will require a large number of doses to be administered to be able to detect any potential safety signals in the Vaccine Safety Datalink (VSD). In the meantime, Vaccine Adverse Event Reporting System (VAERS) reports will be monitored [[1]Costa I, et al. mBio. September/October 2014; 5(5): e10625-14. [2]Granoff D. 2014. Microbe. 9(8):321-327. [3]Granoff D. JID. 2015]. Adverse reactions may occur following any type of vaccine. Shoulder injury related to vaccine administration has been recognized in case reports. The incidence is unknown, though it appears to be very rare. Syncope occurs at a rate of about 1 per 1000 doses and can lead to injuries from falling. Anaphylaxis may also occur following any type of vaccine and occurs at a rate of 0.21 to 1.53 per 1 million doses administered. MenB-FHbp and MenB-4C have each had one case of anaphylaxis reported to date.

The WG's interpretation of the MenB safety data is that post-vaccination local and systemic complaints are common following MenB administration, but the reactions are typically self-limited. The most common AE reported was pain at the injection site. Potentially serious AEs may occur following any vaccine, and should be considered in light of the current low disease burden. To date, no concerning patterns of SAEs have been reported for MenB vaccines. However, theoretical concerns have been raised from animal models about autoimmune disorders and will need to be monitored through post-licensure safety surveillance.

The WG also considered additional data. A cost-effectiveness analysis for routine use of serogroup B meningococcal vaccines was completed by Ismael Ortega-Sanchez of CDC. The full presentation was included in the ACIP members' background materials. This was a Monte Carlo simulation analysis for a hypothetical 4 million person birth cohort and a 2.8 million college cohort. The timeframe for the analysis was 15 years. The analytic horizon was age-specific life expectancy. The discount rate was 3% (0%-5%). Key assumptions of the analysis included age and serogroup B-specific average incidence rates and case-fatality ratios from 1994 through 2013, and initial vaccine effectiveness of 85% to 95%, waning protection was modeled based on available antibody persistence data for MenB-FHbp and MenB-4C with

waning of protection over 10 years, and a vaccine cost per series (2 or 3 doses) of $402 (cost of vaccine + administration + AE + wastage). It is estimated that approximately 15 to 30 cases and 2 to 5 deaths could be prevented with a routine adolescent program at 11, 16, or 18 years of age. A college student only recommendation would prevent approximately 10 cases and 1 death. The number needed to vaccinate (NNV) to prevent either a case or a death is high. Nearly 100,000 to 400,000 persons would need to be vaccinated to prevent one case. Nearly 1 to 3 million persons would need to be vaccinated to prevent a death. The cost per quality adjusted life years (QALY) saved ranged from approximately $4 million to $9 million dollars in this analysis.

Currently, limited data are available on the impact of the MenB vaccines on carriage. In a study conducted in a university in the UK, 31% to 34% of subjects carried any *Neisseria meningitidis* at study entry. No significant difference in carriage was detected between the study groups at one month after vaccination with MenB-4C. However, a modest decrease in carriage was observed during the 12 months after vaccination. In the US, two carriage surveys were initiated in February of 2015 at schools experiencing serogroup B outbreaks. The surveys are being conducted in conjunction with MenB-FHbp mass-vaccination campaigns at these schools. Baseline carriage was assessed during administration of the first dose, and post-dose 1 carriage was assessed during the second dose mass-vaccination clinics. Additional rounds of the carriage study are planned for Fall 2015 at both schools. Preliminary results from studies showed no change in carriage in the student population from baseline to post-dose 1.

Another important consideration for the use of MenB vaccines is breadth of coverage. Genetic and antigen expression data predict that the MenB vaccines should cover a wide range of circulating meningococcal strains in the US, but they will not cover all strains. The immunogenicity data currently available are directed against a few select strains. However, testing against additional strains is planned as part of a post-licensure commitment to FDA by both manufacturers. However, the proportion of the population who will respond to each circulating strain is currently unknown. One example of this is the lower responses that were observed to the Princeton outbreak strain. The currently available data do not allow for prediction of the proportion of the population who will respond for each outbreak or a sporadic disease-causing strain.

In summary, there are a number of challenges to keep in mind when considering the use of MenB vaccines in the US. First, the proportion of serogroup B cases that could be prevented with a MenB vaccine is unknown. Breadth of strain coverage has only been estimated. The actual breadth of coverage is unknown or unclear. Available antibody persistence data suggest that MenB vaccines may have a limited duration of protection. In addition, vaccine effectiveness data are not yet available, as licensure was based on serum bactericidal activity and universal programs have not yet been implemented in any country. The potential impact of the MenB vaccines on carriage is also unknown, as is the potential impact that the vaccine pressure will have on circulating strains.

The WG has considered several policy options for broader use of MenB vaccines in adolescents. Ages for the recommended administration of a MenB vaccine series that were considered included at 11 to 12 years with an anticipated booster at 16 years of age, or a series at 16 or 18 years of age, or a recommendation for college students only. In addition, the WG considered different recommendation types, including Category A, which is a recommendation for all persons in an age- or risk-factor-based group; Category B, which is a recommendation made for individual clinical decision-making; or no recommendation.

After reviewing the data, the consensus of the WG was to support a policy option that included vaccination of all adolescents rather than college students only. The WG's considerations included that an important burden of serogroup B meningococcal disease cases occur in those 18 through 23 years of age who are not attending college. It would be challenging to get students vaccinated with two or three doses before arriving on college campuses, and vaccination of college students would prevent the fewest cases and deaths among the options considered. However, the WG also acknowledged the impact that cases and outbreaks have on college campuses in terms of the cost of vaccination campaigns in response to these outbreaks and public concern.

The WG considered three options for the preferred timing of the MenB series, including at 11, 16, or 18 years of age. Based on the available antibody persistence data, the WG felt that there was a need to administer the MenB vaccine series in later adolescence, preferably at age 18, in order to maximize the likelihood that protection would last into the highest risk period. However, the WG also recognized that young adults may still be under the care of a pediatrician at 16 years of age, but will be less likely to receive care from their pediatrician at age 18. They should also be making a visit to their healthcare provider at age 16 for the MenACWY conjugate booster. Based on these considerations, the majority of the WG members preferred language recommending administration between 16 and 18 years of age. This will also increase the likelihood that the college-bound population will complete the two- to three-dose series before entering college during the highest age-related risk period.

The WG currently favors a Category B rather than a Category A recommendation for two main reasons. First, the current burden of diseases is low. This means that the NNV to prevent a case and death is high, and the number of cases prevented may be comparable to the number of SAEs to vaccine. Second, additional data are still needed to consider a routine recommendation. Most importantly, a better understanding is needed of the true proportion of serogroup B cases that could be prevented with MenB vaccine, including data on vaccine effectiveness and the impact of MenB vaccines on carriage and herd immunity.

The WG recognizes that historically, Category B recommendations for use of polysaccharide vaccine in college students was unpopular and was interpreted as difficult to understand. The 2000 recommendation was that college students and their parents be informed by healthcare providers of the risks of meningococcal disease, and the potential benefits of vaccination with a polysaccharide vaccine. College and university health services were also to facilitate implementation of educational programs about meningococcal disease and the availability of vaccination services. Polysaccharide vaccine was to be made available to those persons requesting vaccination. In several states, this Category B recommendation was translated into legislation requiring colleges to provide information on the risks of meningococcal disease to students or mandate vaccination of certain students.

Finally, there are additional programmatic considerations which the WG discussed such as implementation challenges of a MenB multi-dose vaccine schedule, and that there is no platform for a two- or three-dose vaccine series in late adolescence. The current MenACWY vaccine program in adolescents is at 11 to 12 years of age with a booster at 16 years of age, which makes communication challenging when there are differing recommendations for the conjugate vaccine and the MenB vaccines. MenACWY is not currently recommended for other groups with similar or higher risk, but that may need to be reconsidered if a Category B recommendation is made for MenB in adolescents.

In summary, the Meningococcal WG acknowledged that meningococcal disease is a rare but serious illness and each case is life-threatening. However, important data for making policy recommendations for MenB vaccines are not yet available. There was a strong desire within the WG to ensure access to MenB vaccines, as well as an understanding that work still needs to be done to reinforce the second dose of the conjugate vaccine in the current adolescent program. The risk of meningococcal disease is low. However, cases do occur. It is difficult to accept that, in the absence of a vaccination program, there may be cases that are preventable. However, even with a fully implemented vaccination program, the MenB vaccines will not prevent all cases.

The WG proposed the following language for use of MenB vaccines in adolescents:

> "A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. (Category B)"

In addition, the following language would be provided as guidance for use:

- MenB should be administered as either a 2-dose series of MenB-4C or a 3-dose series of MenB-FHbp
- The same vaccine product should be used for all doses
- Based on available data and expert opinion, MenB-4C and MenB-FHbp may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible
- No product preference to be stated

Discussion Points

Dr. Belongia noted that in the MenB-4C trial, there was an episode of thyroiditis and two episodes of juvenile rheumatoid arthritis (RA) that were thought to be vaccine-related. He wondered if anyone had any information regarding why that was thought to be the case. Given that the vaccine is licensed in multiple other countries, he wondered whether there were any post-licensure data on safety from other countries that could help to understand potential risks.

Ms. MacNeil responded that currently, there are not post-licensure safety data available from other countries. The vaccines are licensed in several other countries, but no programs have been implemented. The United Kingdom (UK) plans to begin vaccinating infants in September 2015, after which there will be more information.

Noting that ACIP tends to avoid Category B recommendations, Dr. Harrison asked what the potential impact of a Category B recommendation would be on cases, deaths, and college outbreaks prevented. For a disease with a relatively high case fatality rate, his sense was that a Category B vaccine probably should be avoided.

Ms. MacNeil replied that a lot depends upon the extent of vaccine uptake and how much coverage there is in the population, which is unknown at this point. There may be mandates or

recommendations for college students to be vaccinated. While that is likely to vary by individual school, coverage probably will be highest in those groups.

Dr. Temte invited Dr. Even to make a comment regarding what role residential colleges and universities would have, and the likelihood that they would either mandate or strongly recommend a vaccine.

Dr. Even (ACHA) indicated that vaccinations can be mandated upon school entry. In general, her observation and experience has been that private universities have a wider range of recommendations that perhaps mirror CDC and ACIP recommendations for college-aged students. This varies broadly among smaller and public universities. Some of them will select certain immunizations for requirement. With a Category B recommendation, a mandated requirement is less likely, but it would probably be part of information campaigns.

Dr. Reingold noted that Slide 3 showed the incidence rates for various meningococcal serogroups, with the declines being indistinguishable for B and the serogroups in the A/C/Y/W135 vaccine. However, Slide 4 showed compelling evidence that a decline in A/C/Y/W135 is limited to the group targeted for vaccination, which was an interesting distinction that was difficult to understand and he wondered whether there was an explanation for that. He also said he was very happy that the workgroup did not opt for a college-only recommendation, given that primarily those who are better-off go to college in this country, which creates an equity issue. To him, the only reason to focus on a college-only recommendation would be if the rate of disease was substantially higher and it clearly is not.

Ms. MacNeil responded that while there have been many theories, the reason is unknown why meningococcal disease rates have continued to decline in the population overall.

Ms. Pellegrini asked for clarification regarding the workgroup's consideration of the dosing schedules beginning at age 11 or 12, and whether that would be two or three doses followed by a booster dose at age 16. The problem is that there is not a platform for late adolescence. Getting any teenager into the doctor more than once a year is difficult. Getting a 17- or 18-year old is likely to result in poor compliance rates.

Ms. MacNeil clarified that it would be a complete series at 11 or 12 years of age. While no data are available yet, it is anticipated that based on antibody persistence, a booster would be needed at 16 years of age. It would be an additional dose.

Dr. Loehr (AAFP) pointed out that if his calculations were correct, there are about 50 to 60 cases in persons 18 through 24 years of age. In a cohort of about 4 million per year, that is about 1 in a million incidence rate. The rate of anaphylaxis is about 0.2 to 1.5 per million doses, and both small studies already each had one case of anaphylaxis. That is, there was one case of anaphylaxis in the study with 11,000 and one case in the study with 60,000. Extrapolating those would indicate that there is possibly a higher rate of anaphylaxis than for other vaccines, based on the available data. That would mean a 1 in a million case incidence and between 17 to 100 cases of anaphylaxis per million.

Ms. MacNeil confirmed that this is what has been observed. However, she did not believe there was enough information to say that rates are higher for these vaccines at this point.

Regarding the policy option and the issue of strain diversity, Dr. Karron wondered with what confidence it could be said that short-term protection against most strains of serogroup B meningococcal disease differ between vaccines.

Ms. MacNeil replied that this is not known for sure. Though tested against only a few strains, the assumption is that a majority of serogroup B strains in the US would be covered.

It appeared to Dr. Gorman (NIH) the recommendation language would exclude 75% of the cases of serogroup B from potential protection. Recommending that individuals 16 through 18 years of age be vaccinated permissively, to use old language, that would be 54 out of the 203 or 67 out of the 260. He wondered what drove the recommendation for that particular age range.

Ms. MacNeil indicated that 80% of cases are occurring in individuals 11 through 24 years of age, with most cases in that age group actually occurring in adolescents 16 through 24 years of age. That was part of the rationale for the recommendation at the later age. There are very few cases among those 11 through 15 years of age.

Dr. Gorman (NIH) wondered why the recommendation was not for less than 5 years of age where there are more cases.

Ms. MacNeil responded that the vaccine is not licensed in that age group.

Dr. Temte reiterated that there is currently no FDA licensure for revaccination. The vaccines are licensed for two or three doses. He asked whether manufacturers were planning to conduct studies pertaining to revaccination.

Laura York (Pfizer) indicated that Pfizer has ongoing studies. They will be boosting individuals who received vaccine about four years ago. Those data are anticipated to be available in 2016.

Leonard Friedland (GSK) indicated that GSK's current attention is focused on a pentavalent meningococcal ACWYB combination vaccine. With that vaccine, booster doses will be studied as well.

Dr. Harriman pointed out that cost-effectiveness analyses must be considered with caution, especially when performed before the widespread use of a vaccine because it is known that the cost can increase or decrease. It is also known that cost-effectiveness analyses favor common but less severe diseases over rare but very severe diseases. The public shows a preference for trying to protect against rare but severe diseases. She would like to have seen some analyses with price points other than the manufacturers' retail prices. Presumably, the UK is receiving a much less expensive vaccine. Cost-effectiveness analyses are extremely sensitive to both cost and incidence. She would like to see better incidence data as well. While she is happy that ACIP has a Category B recommendation that does get paid for, she worries that it may be perceived as a less important vaccine and may not be offered or recommended as often. It is very difficult to explain to a parent whose child has died of meningococcal B disease why a vaccine was available but was not recommended for their child.

Dr. Temte noted that this reflected the GRADE process in that after the evidence evaluation in trying to formulate recommendations into a Category A or B or no recommendation, cost-effectiveness is used. As Dr. Loehr pointed out, the balance of benefits and harms are assessed in terms of potential adverse effects. Consideration also is given to the values and preferences of stakeholders, liaisons, and the general public. It is good, with the known unknowns and unknown unknowns, with this vaccine going forward to have a variety of options there in terms of making recommendations.

Dr. Kempe emphasized that given the potentially small benefits, potential risks must be considered very carefully. She would like to know more about why the cases of thyroiditis and RA were related to the vaccine.

Dr. Schuchat indicated that CDC did not have more details on that, but the manufacturers may have those data.

Dr. Friedland (GSK) did not have further information about the three cases. GSK has been following over 45,000 patients in post-marketing studies for vaccines that have been used inside and outside of the US. No signals have been observed related to the concern about autoimmunity. They will continue to follow this very closely in all of the trials throughout the world.

Dr. York (Pfizer) stressed that this is always a concern, particularly in the adolescent population. Under Pfizer's clinical trial, the FDA reviewed all of the data that were available and did not see a signal.

Dr. Baker (IDSA) pointed out that the problem is the denominator. It is unknown whether this is going to stay flat for 3 million people versus 3,000 or 11,000. The beauty of Category B is that there are two FDA-licensed vaccines, and the appeal to her is that individual physicians or parents or of-age young adults can have a discussion regardless of whether they are under the VFC program or would not have the funds to pay for the vaccine out of pocket. As noted earlier, this age group is not necessarily attending college, so the equity issue is addressed through a Category B recommendation.

Dr. Temte emphasized that a Category B recommendation automatically falls under the VFC and the ACA. A Category A or B recommendation avoids creating inequity. Alternatively, making no recommendation creates a situation in which people who can afford the vaccine can get it and those who cannot afford it will choose not to get it.

Dr. Moore (AIM) stressed that there are many unknowns regarding how well this vaccine is going to perform. Regarding the spread of the short-term immunogenicity results in the RCTs, she was perturbed by seeing 63% to over 90%. She wondered if there was a biologic explanation for such a spread in those results. From a programmatic standpoint, AIM will be considering how to implement Category B recommendations and how they are presented in IISs. From the program standpoint, they want to try to understand how best to convey the intention of the committee in terms of vaccine forecasting with IISs. What will they say when a 16-year-old comes in? Should it be left off of the forecasted recommendation list, or listed somehow differently? It is not clear yet how to show that a Category B is a permissive recommendation.

Ms. MacNeil indicated that the data from the hSBA came from three strains or four strains. On the higher end, some of the studies were conducted in populations in which the epidemiology is quite different from in the US. For example, about 20% of the people had a baseline titer, which probably indicates high levels of carriage. Some may have had some pre-existing immunity, which may increase that. Compared to populations that are more similar to the US, it is somewhat lower.

Dr. Grogg (AOA) reminded everyone that as a practicing clinician who receives calls in the middle of the night during influenza season and the rapidity of the illness of meningococcal disease, he feels much better counseling patients if he knows they have had a meningitis vaccine and are current on all vaccinations when a 102^{o} temperature and muscle aches are reported.

Regarding the persistence data, Dr. York (Pfizer) emphasized that there are differences in populations. The backgrounds can make a difference in terms of the actual results and the way those results are presented. The approaches that are taken to show breadth of coverage or the response to the vaccination antigen will, perhaps, make an impact on that. Pfizer's approach is to assess the response over time in a study that started in a number of countries very early in order to assess the responses that are predicted in various populations. In the data from a number of studies in different countries, the range of responses against the four strains that are representative are very consistent. Therefore, they believe the persistence will be consistent.

Dr. Schuchat pointed out that the short-term immunogenicity results differed not only by country or study, but also by the populations which were different ages. She wondered within the studies if there were any age-related differences in the short-term immunogenicity. The UK had the highest results, but they had the older population.

Ms. MacNeil did not think specific age-related differences were assessed within the different populations. The reason that the UK study was included in the package insert was because it had data for older adolescents; whereas, no other study was conducted in the age group. The Canadian and Australian data were included as well for the younger age group because they were thought to be the most representative of US populations.

Ms. Pellegrini noted that the debate was crystalizing for her the challenges associated with conversations that were also occurring in the health policy world pertaining to the differences that exist in the types of data that are necessary for FDA licensure versus an ACIP recommendation. While she understood the tremendous challenge for drug makers to try to prognosticate what the data are and how to acquire it, with the more frequent use of the FDA-expedited pathways and alternative pathways for approval, this is going to be an increasing issue with vaccines in the future.

Dr. Paradiso (Vaccine Consultant) reminded everyone that a composite response rate meant a response to all of the strains tested. A response rate of 90% for each strain means that by the fourth strain, it is 90% of 90% of 90% of 90%. It is not going to be 90% of a composite. He was hearing some push and pull on the A and B category, with a leaning toward the B category and the hope that people will still use the vaccine. He heard the question regarding whether colleges would mandate the vaccine or recommend use with a Category B recommendation, with the hope that they would. However, a B category recommendation would make that less likely to occur.

Dr. Zahn (NACCHO) expressed concern that the recommendation states that the recommended age range is 16 through 18, but it can be given at 16 through 23 years of age. It was not clear to him how providers would interpret that. Short-term protection was also confusing to him, because that implied that there was a short-term period of time when he should choose to vaccinate. While the goal seemed to be to make people aware that coverage would not last that long, he did not think of that as being part of the recommendation. He agreed that making it a Category B would make it very difficult for a provider to interpret the information.

Dr. Riley said that as the parent of one college-aged child and one child who just finished college, she was completely unclear about what the WG expected parents to do. If she or her daughter goes to the doctor and indicates that they have heard there is a vaccine that will protect her daughter from a deadly disease, they would have to rely on the doctor to make a value-based judgment about whether she should receive this vaccine. This kicks it back to the 19-year-old who is going to call her mother, who is just as confused.

Dr. Baker (Physician) said that as a WG member since 2003, Ms. MacNeil made one of the best presentations of the data she had ever heard. The data are frustrating. The vaccine is known to be protective short-term for at least 2 years, but that does not mean protection will not last for 5 to 10 years. This is a deadly disease, the cost-effectiveness analysis is terrible, but there are licensed and available vaccines. She agreed with Dr. Riley that an individual practitioner may have some difficulty in knowing all of the innuendos to counsel her or one of her daughters, but the vaccine will be available and will be paid for in an equitable manner. However, unlike huge health maintenance organizations (HMOs), it has been her experience with permissive recommendations in the past that smaller practices may not even carry Category B vaccines in their offices. While practitioners can council patients, the patients may have to go elsewhere to be vaccinated. Individuals should be allowed to have these vaccines paid for, either by their private health insurance company or by the VFC.

Dr. Temte emphasized that as they have shown fairly recently, ACIP can make rapid changes in the recommendations based on emerging information.

Dr. Harrison thought there was potential for inequity with a Category B recommendation, which could occur in terms of how knowledgeable a practitioner is about meningococcal disease.

Dr. Campos-Outcalt thought a Category B recommendation was acknowledgment of the fact that in the future, with more vaccines against rarer diseases, they would not be able to recommend every vaccine for every person every time. There will have to be intermediate recommendations, and he thought Category B would fill that need. The vaccine is available. People can get it. They want to make it equitable, but they were not convinced at this point that every person should receive it. If the only option was a Category A recommendation, he would be forced to vote against this vaccine based on the data. Putting this into perspective, if even half of the cohort is vaccinated at the predicted cost, this would mean adding $2 billion to the VFC budget. CDC's entire budget is $7 billion. There are 20,000 to 30,000 deaths a year in this country from mental health-related diseases in the same age category. The entire budget for SAMHSA is $3.6 billion. Adding a Category A recommendation would exceed SAMHSA's entire budget. The world is bigger than just vaccines and vaccine-preventable diseases. To him, a Category B was a good option at this time.

Dr. Kimberlin (AAP) added that as he understood it, a Category B vote would encumber the dollars from VFC, assuming a VFC vote was approved. Assuming the numbers were correct, that would be $2 billion from the VFC funds. He did not think a Category B recommendation would keep that from occurring. He thought sometimes it was better to do nothing and wait for a while.

Dr. Belongia did see a benefit in a Category B recommendation because it acknowledged the fact that ACIP does not have all of the answers at this point. Important questions remain that need to be addressed. However, usage will certainly increase due to a recommendation and that would allow for collection of additional observational data to further assess the safety and the impact of the vaccine in the population. While even one death due to serogroup B is too many deaths, they have to acknowledge that they have a responsibility also to ensure that they do not make recommendations that ultimately might be shown to have unanticipated harmful effects.

Dr. Rubin thought that a Category B would be appropriate because fundamentally, it would send the message that there is a balance between the benefits and risks of the vaccine that each decision-maker should take into account.

Dr. Hahn (CSTE) pointed out that with a Category A recommendation, many states will mandate the vaccine for school entry. Many states currently have kindergarten entry and seventh-grade requirements. With the lack of data, it would be a challenge to mandate the vaccine for school entry and could promote some backlash.

Dr. Middleman (SAHM) voiced the Society for Adolescent Health and Medicine's (SAHM's) support for a Category B recommendation.

Dr. Dwelle (ASTHO) expressed concern about the potential autoimmune factors. The incidence of thyroiditis in the US ranges from 12.1 to 24 per 100,000. Calculating that back to the 3,100 reported, a maximum of up to .74 would be expected. There is a question about the safety of the vaccine as well.

Ms. Stinchfield (NAPNAP) acknowledged the importance of the use of the vaccines for outbreak management and that local public health and colleges have to be prepared in advance to use the vaccine. Education of clinicians, adolescents, and parents about the signs and symptoms of meningococcal disease and early recognition, early treatment, and prompt community response may be one of the most important efforts they could make with regard to this disease.

Dr. Romero emphasized that it is the responsibility of physicians to educate themselves on the risks and benefits of vaccines. Physicians must understand the risk of the disease and make recommendations as appropriate for the child. If there is a vaccine that works, it should be ACIP's job to educate their colleagues and promote its use if a Category B recommendation is made.

PUBLIC COMMENTS

Dr. Temte reminded everyone that approximately 40 letters were received regarding this topic, and that all ACIP members were provided with copies of the letters. The letters were from universities, colleges, Chancellors of large systems, student health, and public health departments, student-government organizations. The National Meningitis Association (NMA) provided a document with over 1000 signatures, and Meningitis Angels provided a petition with 601 signatures. Due to lack of time, Dr. Temte was unable to read all of the letters into the official meeting minutes but indicated that they would be included as part of the minutes. The letters are appended at the end of this document.

Dr. Steven Black
Pediatric Infectious Disease Specialist and Vaccinologist

Thank you for the opportunity to speak. My name is Steve Black, and I've been a Pediatric Infectious Disease Specialist and Vaccinologist for more than 30 years. I guess I want to make two disclosures. I'm a consultant for GSK, Protein Sciences, Takeda, and WHO. And secondly, I really hate this disease. I've seen many children and adolescents who have died or whose lives have been ruined by meningococcal B disease, children and adolescents who are completely healthy and had the potential for a long and happy, productive life. This disease changed my life also. I was a third-year pediatric medical student, and my first rotation was pediatrics. One of the first patients I saw was a girl named Laurie who had meningococcal sepsis and was admitted to the ward. On the third day of the hospitalization, the resident I was working with was walking to another hospital to take a call and didn't show up and was found dead on the sidewalk subsequently of meningococcal B disease. I think, prior to that time, I was planning on being an echocardiographer. Actually, the first paper I ever published was a cardiology paper. But this disease really changed my life and made me want to go into infectious diseases. It's now more than 40 years later, and we now have the possibility of prevention of this disease. Since meningococcal B disease is rare as we've heard, we're told that perhaps it's not cost-effective to prevent the hundreds of cases that still occur in this country. I think the people that say that, as was said by others, are considering these cases as numbers and not people. They're not seeing them as people and their families. They're not seeing the suffering associated with this disease and, really, the misery due to complications as well—not just deaths—in terms of amputations, blindness, et cetera that occurs. So cost-effectiveness really, as has been said, and the GRADE criteria provided should not be considered alone as a criteria here for making decisions. Additionally, cost-effectiveness analyses that are performed prior to implementation really have not had a great historically predictive value. I was before this committee when the pneumococcal conjugate vaccine was considered. At that time, the cost per QALY was $85,000 or $90,000 per quality-adjusted life-year. There were several people on the committee who said that this was really not a cost-effective prevention. As we know now, after vaccine introduction, this is now one of the more cost-effective vaccines that we have. So, I became a doctor to save lives, and I think that it’s difficult to save lives one on one, especially with meningococcal B disease, where it evolves so rapidly. And sort of one of the greatest fears of pediatricians and parents is to miss a case of this disease because, once it commences, the risk of sequelae and mortality is so high. So, I think the committee has an opportunity today to prevent these deaths, to prevent the suffering and loss of life potential in dozens of children each year, and I would urge the committee members to seize that opportunity and to routinely recommend this vaccine for children. Thank you.

Frankie Milley
Mother of Ryan Milley
Founder / National Director, Meningitis Angels

Hi my name is Frankie Milley. I'm the mother of Ryan and the Founder and National Director of Meningitis Angels. Monday, 17 years ago, I carried my only child into an emergency room, screaming, "He has meningitis." Within two hours, there was blood coming from every orifice of his body, and I watched him die a horrible death. The last words Ryan heard were from his dad. "Daddy loves you, baby boy." The last words Ryan said were, "I know." I will never be the parent at a college graduation. I will never dance with my son at his wedding. I will never hold a grandchild, and I won't have the care of a child in my old age. The stats that you have are not necessarily correct, and we know that because all the cases don't get reported because it costs money, and some hospitals and some health departments don't want to spend that money or don't have it to spend for those reports. We know that kids are misdiagnosed when they come into the emergency room or they're given antibiotics and once that antibiotic hits the bloodstream, it's no longer diagnosable. Ryan's cause of death was Waterhouse–Friderichsen syndrome (WFS). On the fifth day amended lab report, it was Group C meningococcal. I've been coming to these ACIP meetings for 12 years. I've testified at almost all of them, almost 36 times. For a total of 108 minutes, I've been allowed to speak about my son and the importance of immunizing kids. In those 12 years, the working groups, the ACIP voting committee, and us old warriors that are here every time have come very far. We've left here celebrating, and we've left here crying. One of the worst was when we had a vaccine to prevent meningococcal B in infants and we didn't get a recommendation for it. We still have parents calling us every day who have infants and children, "Why can't we get our kids vaccinated? Why are our kids dying? Why is my child so mutilated? Why couldn't I get that vaccine?" We know that permissive recommendations don't allow for education of the disease and the vaccine. We know, in many cases, there's no affordability or accessibility. We know that there's a hesitancy of physicians and healthcare providers to give it because it's really not recommended or it's permissive. We know that there is provider reimbursement problems with a permissive recommendation. One thing this does is it really confuses parents about: Is my child fully protected or are they not fully protected? One of my parents right here in Georgia sent her 17-year-old who is about to go to college this fall to her pediatrician to get her meningococcal B vaccine. Guess what? They gave her the conjugate again, the second one she's had in two years, because they don't know. They are not educated. There's no real information out there.

We are still seeing outbreaks in Oregon and the gay community. We're seeing outbreaks on college campuses. We're seeing random cases of adolescents. We still see toddlers and infants die with this disease or be left terribly mutilated. Again, I want to remind you, this, to me, is like having a ship that's sinking. You have 100 passengers, 100 life vests, and you only give out 50, and the other 50 people on that boat drown as they watch their life vest hanging in the closet. How many tears do we have to cry and how many children and young adults have to be debilitated or die before we make this and we do the right thing and just stop this disease? I want to remind each and every one of you that look at stats, I know you have to do that, but each one of those stats, each one of those cases represent somebody's child, somebody's life. It represents a child or young adult who has lost limbs, faces, are blind or deaf, and live a really hard life. They represent parents who have gone through a divorce and financial and social ruin in their lives. Some of them watch their kids every day who suffer from seizures and all kinds of problems and never know if the next day their child is going to wake up or not. This is the life that I live with all of our families. Each one of those numbers that you talk about represent somebody's child. Just remember that. So you know, permissive recommendation—

I'm disappointed. You know, I would like to think it's a real step forward. But unfortunately, I think it's going to cause a lot more confusion in our world and among parents and physicians and payers. Thank you to the committee for your dedication and your hard work. I know that you don't have an easy job. I know you're all parents and grandparents. Dr. Temte, I especially wanted to say to you, you've been an amazing leader, and thank you for your care and your kindness and consideration of all of us.

Scott Parkhurst
Father of Jacob Parkhurst

Thank you for letting me speak. Hi. My name is Scott Parkhurst. I'm from Portland, Oregon. My youngest of two sons, Jacob, was a 17-year-old junior in high school. Jake was an A student and was a member of the high school swim team. He also enjoyed snowboarding, golfing, and riding motor cycles. He was my mini-me. Jake would have graduated high school a few weeks ago. But, that was all taken away from him last year. It tears me up seeing his classmates enjoying graduation and getting ready to head off to college. This should have been one of Jake's shining moments. Fifteen months ago, on a Sunday afternoon, Jacob said he didn't feel well. By Monday morning, he was in the emergency room. The ER doctor pulled Jake's mom and I aside and informed us that Jake may not survive and appeared to have bacterial meningitis. I told Jake to fight for his life and he yelled back to me, "Okay" as he was taken off to intensive care and put into a medically induced coma. That was the last contact I ever had with Jake. On Tuesday morning, the doctors ran an EEG to check his brain activity. At that point, they determined he was brain dead. In 36 hours, my son was dead. Cause of death: bacterial meningococcal, serogroup B. Every day, almost every hour, I have thoughts of Jake. A lot of times it hurts real bad, especially when I hear of another person becoming sick with meningitis. I end up reliving the final tragic moments of Jake's life. This has affected everyone in my family. We have had to deal with depression, marriage counseling, alcohol, drug use, and rehab, to name a few. It completely turns your world upside down. My oldest son, Jeff, was heading to OSU in September and planned to live in a dorm. We were all terrified of him possibly contracting meningitis. Thanks to Alicia Stillman and her interview on the *Today Show*, I followed her lead and took Jeff to Canada to get the serogroup B vaccination. We shouldn't have to take our children to other countries to get vaccines. The most recent outbreak at U of O has hit home, as this is my home state and I have lots of friends and family that have children attending U of O. Fortunately, they have all been vaccinated. But at this time, only half the student body has been vaccinated, and it's been over five months. The permissive recommendation doesn't cut it. It creates an inequality and just creates a lot of confusion, and I just don't feel that's effective. I understand this disease only affects a small percentage of the population. But when it's your son, daughter, grandchild, cousin, niece, or friend, it's 100%. I don't think anyone here who has children would want to lose their child to something that is preventable. I strongly encourage the panel to make a routine recommendation and stop the spread of this deadly, debilitating disease. Jake didn't get that chance. Thank you.

Alicia Stillman
Mother of Emily Stillman
Founder / Director, Emily Stillman Foundation

I am Alicia Stillman, and I thank you very much for giving me the opportunity to speak here today. I'm here as Emily Stillman's mother, and I'm also here as the founder and the director of the Emily Stillman Foundation. This is my Emily. She's 19 years old forever. She's beautiful, she's talented, she's smart, and she was a 19-year-old college sophomore. Emily was not a part of an outbreak. She was a one, and all she had was a headache. She called me one night, "I have a headache." I said, "Why do you think you have a headache? I bet you're coming down with the flu." She said, "No, mom, I was up all night studying for two big tests. But don't worry. I did good." I said, "Great, so take a couple of MOTRIN® and we'll see how you feel in the morning." The morning never came. By the time I was called back to the hospital the next day and told to get en route immediately, Emily was in a coma. I never saw the gorgeous eyes open. I never saw her look at me, tell me she loved me ever again. My favorite thing about Emily was when she would hug, she would hug with her whole body. It wasn't like limp arms around you. And now, when I want a hug, it's a cold stone. This is what I hug when
I hug my daughter now. Emily happened to have been my daughter, but she could have been any of your daughters. She could have been any of your grandchildren. She could be your next-door neighbor. She wasn't a number. She was a person with a future, a wonderful future ahead of her. Last weekend, Emily would have graduated from college. So, instead of being here today listening to "B, A, permissive, not permissive, are we going to let kids get protected, are we going to let parents protect their families" I should be moving my daughter to a new city to start her life. Would she be starting grad school? Would she be on the stage? Would she be starting a new job?

Instead, I am begging you to protect our kids. To give parents the ability to vaccinate their children with a vaccine that wasn't protecting my daughter. I made my daughter a promise when I said goodbye to her. I promised her I would be her voice. I promised her, "I don't know how this could happen. You were protected. I did everything I was told to do, but I will figure out how this could happen and I will make sure it doesn't happen to other people." When I formed the Emily Stillman Foundation, that was my mission and that's what I did. And yes, before our FDA approved those vaccines, I schlepped busloads to Canada and I protected whole families in Canada with this vaccine. Now we have it here and I field phone calls and emails all day long from parents all over the country who can't get their hands on this vaccine. Their doctors say they don't even know that there's one approved. They don't even know it's approved. That's what they tell them. "Oh, but don't worry. Your kid doesn't need it." So with a permissive vaccine, who will pay for it? Who will carry it? I worry about that. I worry that in 2015 we're going to become communities of have and have-nots and knowledge and knowledge-nots. And that's not okay. I have letters here that I know you've all seen, in my folder, from every university in the State of Michigan: University of Michigan, Michigan State, Kalamazoo College, Wayne State School of Medicine, Central, Northern, Eastern, Western. I know you've all seen them. They all want their campuses protected. Emily isn't a number. A one doesn't matter. When it's your child, a one might as well be a million. And I'll close just by telling you that, in Judaism, we are taught, "To save one life is like saving the whole world." And you are taxed with that. You are taxed with that today, so please save the one and save the world.

Mike Barnes
Father of Jimmy Barnes
National Meningitis Association

My name is Mike Barnes, and I am here today as a representative of the National Meningitis Association. I'm joined by my wife, Charlene, and my daughter, Kendall. We lost our 20-year-old son, Jimmy, to serogroup B meningococcal disease this March. He went to the ER on a Monday with a terrible headache, neck pain, and high fever. He was told it was the flu and sent home. He was gone in 28 hours. He was not a college student living in a dorm, and his story was not covered by the media, so I'm here to share it with you today. He was, however, we thought, fully vaccinated, including with the meningitis vaccine. Charlene and I were not able to have our own kids. It took many years, but eventually, we were able to adopt Jimmy when he was three days old. Five years later, we adopted our daughter, Kendall. We had the perfect family. We had a great life. Jimmy was a great kid. He was always joking and smiling. Everyone liked him. He had a million friends. As a parent, it seems as if childhood lasts forever, but those teenage years fly by. First he's struggling with homework. Next, he's learning to drive and applying to college. Jimmy chose Colorado State University to be near skiing, but he found the work load overwhelming and decided to return home to New Jersey. We were glad to have him back. Shortly after his return, our family moved to Florida. He loved the beach life, and he made a million friends just like he always had. Jimmy and Kendall were always very close. They were so protective of each other. They loved each other very much. They were more than brother and sister. They were good friends. Kendall will feel this loss for the rest of her life. There are now so many things I don't have to worry about anymore, like when he's coming home at night or what kind of job he'll get or if he's getting enough sleep. I don't know what kind of man he would've turned out to be. I won't be able to bounce his kids on my knee or take them to the beach. I can never hug him or tell him I love him ever again. Jimmy made our world a brighter place. His light is out, and we wonder if the world will ever be as bright again. In my family, among my two children, the incidence of men B was 50%. For Jimmy, it was 100%. Today you have ability to make sure no other parent has to stand here and share a story of how their son or daughter died. On behalf of my son, Jimmy, who is no longer here, I implore you to extend the current vaccine recommendations for adolescents to include a vaccine to prevent meningitis B. Thank you.

Theresa Wrangham
National Vaccine Information Center

Dr. Temte indicated that an effort had been made to permit a letter to be read into the record by telephone, but after a discussion with the Management Analysis and Services Office (MASO), the decision was made for Dr. Temte to read the letter for the record. He apologized to anyone who found this to be unfair, but explained that it was an intermediate step.

"Thank you for the opportunity to provide public comment today. Founded in 1982, the nonprofit National Vaccine Information Center advocates for the institution of vaccine safety and informed consent protections and public health policy and laws. We support the availability of all preventive healthcare options, including vaccines, and the right of consumers to make educated, voluntary healthcare choices. Meningococcal disease is devastating to those stricken, and the public has the right to use MenB vaccines. As the committee considers routinely recommending MenB vaccines, please consider the following information. The current US population is estimated to be over 321 million. According to CDC, meningococcal disease in the US ranges from 800 to 1200 cases annually. One-third of these cases are serogroup B, with 60% serogroup B cases occurring in children too young to benefit from the MenB vaccines.

The CDC also has acknowledged that humans are the only natural reservoir for *N. meningitidis*. As children grow into adulthood, the vast majority have bactericidal antibodies against this disease. Accordingly, a CDC report published in 2000 revealed that routine recommendation of meningococcal vaccines for college freshmen living in dormitories was not cost-effective. The report stated that it would take 300,000 to 500,000 doses of vaccine annually to prevent 15 to 30 cases of disease and one to three deaths. The costs were $600,000 to $1.8 million to prevent one case of disease and $7 million to $20 million to prevent one death. Although this report precedes licensure of MenB vaccines, MenB vaccine cost-effectiveness findings would be similar. Because ACIP's routine recommendation often translates into legal vaccine mandates in many states, choice in recommendation versus vaccine requirements were unifying themes noted in CDC's 2011 stakeholder report by meningococcal vaccines. We have listened with deep sympathy to the experiences shared by parents whose children and family have been devastated by invasive meningococcal disease. During ACIP meetings and the CDC's 2011 public engagement on meningococcal vaccines, some parents and their healthcare providers did not make themselves aware of meningococcal vaccine availability. These parents have a right to know about the benefits and risks and availability of meningococcal vaccines so they can make an informed decision for their children. However, with regard to ACIP recommending that all children get MenB vaccines, the data is clear that a universal-use recommendation is not justified. It would have far-reaching consequences that will be costly and unnecessarily burdensome to parents, adults, and government agencies. NVIC respectfully requests ACIP to vote against MenB vaccine universal-use recommendation. We encourage ACIP and the CDC to revisit stakeholder report and need for greater flexibility in the ACIP recommendations.

Laurie Stelzer
Mother of Sara Stelzer
National Meningitis Association

Hi. My name is Laurie Stelzer. I'm a representative for the National Meningitis Association. In October 2014, I lost my smart, funny, confident, and very healthy 18-year-old daughter, Sara, to serogroup B meningococcal disease. She called us from her school in San Diego, California complaining of flu-like symptoms. The next morning, her severe headache prompted her to go to the ER. We got there in three hours, but she was already in the ICU on a ventilator and in a coma. By that evening, they thought she was brain dead. She died from serogroup B meningococcal disease just a few days later. Sara donated her organs to save the lives of others. Sara loved to laugh and sing. Even though she only sang in the car, she surprised us and auditioned to sing at her high school graduation. She chose the song "I'll Stand By You" and brought a stadium of people to their feet. She was just beginning her life, and we expected a great future for her. Serogroup B meningococcal disease stole that from her. No mother should have to bury a child. It's just not the right order of things. If one fewer child dies of this preventable disease, that would be a very strong legacy for Sara. I took her for all her recommended vaccines. We got everything they told us to do. At that time, serogroup B vaccines were not available. They were not approved, but they are now. It would be devastating for one other child to lose their life, knowing that it could be avoided. You have the opportunity to prevent other families from going through what we went through. The available vaccines to protect against serogroup B meningococcal disease must be recommended broadly for all adolescents, just as the ACWY vaccines have been. This disease destroys families and lives. Protecting our children against all strains of this life-shattering disease is really the right thing to do.

Jacquelynn Ross
Sister of Stephanie Ross
National Meningitis Association

I just want to thank you for the opportunity to let me speak today. My name is Jackie Ross and I'm the sister of Stephanie Ross, the Drexel University student who died from meningitis B in March of 2014. My sister was awesome, smart, funny, and compassionate. But I'm here representing the National Meningitis Association. I'm here to do what I can to prevent the kinds of losses that so many of us have had to endure. My parents spoke to you in October. On behalf of my parents and also on behalf of all of Stephanie's and my own college classmates who want to be protected from the devastating effects of all the meningococcal strains, I'm asking you to, please, make a broad vaccination recommendation. Since December, my parents have worked to get me the serogroup B vaccine. This was no easy task. It took many phone calls and e-mails between them, the vaccine manufacturers, my pediatrician, various pharmacies, and even the Department of Public Health. I was finally able to get vaccinated just last week, but the process took nearly six months and it only occurred because our pediatrician finally thought to recommend that we look into a travel vaccination clinic. My parents also tried to get the vaccine through several pharmacies. Most did not have the access to it, and those that could get it did not have anyone on staff that could administer it, so ordering it would not have mattered. Parents should not have to work this hard to get an FDA-approved vaccine to protect their children. When you've lost a family member, you go the extra mile to do what it takes to protect your family. My fear is that a lot of people will feel uncomfortable not getting the vaccine through their doctor or that there will not be enough outlets for everyone to get vaccinated. Without a broad recommendation from you today, doctors won't recommend that young adults be vaccinated against this deadly threat. That would be a terrible thing that would sadly only be reversed after more people like my sister suffer the devastating effects of serogroup B meningitis. In the span of a few hours, I lost my only sister, my mentor, and my best friend. I don't want that to happen to anyone else.

Sister of Andrea
National Meningitis Association

I am here because my sister passed away nine months ago. My sister's name was Andrea. She was one of those kids who excelled at everything. From a very young age, she won awards as school, played sports, and still somehow managed to have a social life. Like most college-bound kids, her first question when she got into Georgetown's pre-med program was, "How am I going to afford this?" It turns out she didn't have to worry about it because she was awarded the Gates Millennial Scholarship, but Georgetown actually offered her a full ride. So, she had a lot of potential and she would have been an amazing doctor. In September of her Sophomore year, after a few days of feeling sick and being misdiagnosed as having a viral infection, she was found in her dorm room in a coma and unresponsive. The next day my sister passed away from serogroup B meningococcal disease. She was 19. Seeing my sister in a coma was one of the most traumatic experiences I've ever had. I remember begging her to wake up. I stayed with her until they finally took her off life support until the end. The only way I know how to describe losing her is like trying to breathe with just one lung. I struggle every single day. It's been nine months, and I still struggle to move forward with my life and so do my parents. I'm so glad there's a vaccine now, but it won't save lives unless it's used. As a college student who was not aware of this disease, I just assumed my sister and I were protected. I know that, unless a doctor specifically recommends a vaccine, college students are unlikely to get it or know to ask about it. It was Andrea's dream to help people as a doctor, and making sure that other people get vaccinated would mean she did just that. Please make sure no one

else has to go through the heartbreak our family has gone through and provide a broad recommendation for this vaccine. It's the right thing to do. Thank you.

Lynn Bozof
Mother of Evan Bozof
President, National Meningitis Association

I'm Lynn Bozof, President of National Meningitis Association. Many of you had heard me talk about losing my son, Evan, to meningococcal disease 17 years ago and it doesn't get any easier. About a month ago, my younger son, Ryan, who is a physician in Atlanta, called on his way to the ER with a 104.5 fever and the worst headache imaginable. You all know what I thought. Ryan is fine, but for a few hours, all I could think of was, "I can't go through this again. I can't lose another child to meningococcal disease." It was a horrible déjà vu. Meningococcal disease has scarred my life forever. Seventeen years ago, I didn't know the devastation that this disease could wreak, but I know now. In my role with the National Meningitis Association, I see and I hear it daily. You've already heard from a number of advocates who know it all too well, from siblings who have not only lost their best friend, but have lost part of their parents who are going to be forever grieving the loss of a child; from parents who bravely soldier on and share their stories so that this doesn't happen to any other family; and from survivors who bear their physical and emotional scars with grace and dignity. A handful of our adolescent survivors have submitted written testimony and it's in your packets, and there are copies on the back table for everyone to see. About two weeks ago, NMA issued an open letter and invited people who had been affected by meningococcal disease or who were interested in broad MenB recommendations to sign an open letter. As of this morning, we have almost 1240 signatures from all 50 states. It's been an overwhelming response. We have gotten so many touching, heartbreaking comments from MenB families I didn't know existed. We've captured about 20 of them. They are in your packets. There's also a link if you want to read all of them, and there will be copies on the back table. You have the power to prevent other families from going through this. We can protect our children. We need to protect our children. It's the right thing to do. Thank you.

Andy Marso
Meningitis Survivor

Thanks. So my name is Andy Marso. I'm a meningitis survivor. I'm here on my own time, and my own dime, and I have no conflicts. Last time I was here, I was wearing a suit, but honestly, it's really hard for me to tie a tie anymore. Plus, I thought it was kind of important that all of you see what my arms look like now, because they didn't always look like this. So, you all remember last year when there was this really awful infectious disease going around and all kinds of people were really clamoring for a vaccine? Remember Ebola? Well, what I found interesting about the Ebola scare is that meningococcal B infections are far more prevalent in the United States. They are more contagious. They have a similar fatality rate in the US. Generally speaking, they kill people more quickly than Ebola does. So, based on the general US public's reaction to Ebola, I think it's pretty safe to say that if all Americans understood the gravity of meningococcal B infections, there would be even more people backing me up here as I urge all of you to adopt a broad vaccination recommendation—a Category A recommendation. Unfortunately, most people don't know how afraid of this disease they should be. I know because 11 years ago, I went from a perfectly healthy college student to almost dead within 24 hours. Then I spent four months in the hospital having my skin debrided and parts of my limbs amputated. As I told you all a few months ago, the first year of my medical bills were almost $2 million. That's just for the initial year. $2 million. That would've bought a lot of vaccines, right?

And that doesn't even account for the year of work that my parents missed and that I missed as I was recovering, nor for the ongoing medical costs that I've had every year since. I've been fortunate to have health insurance, but I've basically maxed out my out-of-pocket every single year and I probably will for most of my life. I've accepted that. Again, I know there's concerns about the cost of these vaccines, but I hope you're accounting for all of the costs of not vaccinating and you're also accounting for the cost burden and who bears the cost burden. Is it society at large, or is it just families like mine?

To this point, we've gotten off the hook for a lot of medical expenses due to meningococcal B infections because 15% of those who get them die quickly, which saves us money. But as critical care continues to improve, how many of those will survive, but survive with costly, lifelong injuries like mine? We also know that every year more and more Americans move from rural areas into cities. Isn't it logical that we'll see more outbreaks of this disease as more people cluster together in population centers? We're already seeing an outbreak right now in Chicago, for instance. A meningococcal B vaccine for college campuses has already proven ineffective. As we saw at the University of Oregon, it takes weeks or months to ramp up a mass vaccination campaign. If you wait until a second or third case before you start, you're just inviting unnecessary deaths in the interim. In Oregon, it was the fourth case that proved fatal. Meanwhile, you have an entirely different recommendation for the quadrivalent vaccines, which is confusing and frankly paints you into a bit of a corner. These new vaccines prevent the same disease with the same horrible effects as the quadrivalent. The data shows they're safe and effective. If you hand down lesser recommendations for these new vaccines, we will know that it's strictly for economic reasons so that the government and the insurance companies can save a few dollars. But will the government or insurance companies compensate families who lose unvaccinated loved ones to this disease? Will they compensate families like mine? How would that change the economic equation if they were forced to?

As we've heard, England now has meningococcal B vaccines in its national health program, meaning any British citizen can walk into any doctor's office and get the shot without paying a dime out-of-pocket. They found a way to afford that. Why can't we? By the way, their government negotiated with the drug companies for a price of 20 British pounds per shot. Unless I'm doing the currency exchange way wrong, that's a lot less than $400 American. So with all due respect, I think your cost-effectiveness study is bunk and you should pretty much just disregard it. If you hide behind that as a reason for lack of a recommendation, I think that's going to be pretty cowardly. Are you going to set up another situation like we had when we were waiting on FDA approval in which Americans are second-class citizens globally when it comes to preventative healthcare? Americans used to lead the world on scientific issues. When JFK said, "We're going to send a man to the moon by the end of the decade," he didn't then say, "But only if it's cost-effective." When Jonas Salk was developing the polio vaccine, I don't think he ever said, "Gee, I sure hope the cost of this shot is offset by what it saves in medical costs. Otherwise, this will all be for naught." No. They said, "We're going to send a man to the moon. We're going to wipe out polio" and they did it. They inspired an entire generation of scientists. I don't hear a whole lot of that boldness from this panel today. What I hear is a lot of fear and a lot of hedging. I hear a lot of doctors who seem to want people to be vaccinated, but don't want to take the responsibility for being the one to tell them to get vaccinated.

I need your help. Since I've survived meningitis, part of my purpose in life has been to make sure others don't get it. So I have spoken to as many school groups as will have me, and I've testified in several different state legislatures. I wrote a book. Every time I hear about another person getting ill with this disease, it strikes me right in my chest. What if I had done more? What if I had talked to more people? Maybe my warnings would have reached that person. Maybe that person would have gotten vaccinated or not shared that bacteria-ridden cup or recognized the symptoms and gone to the hospital in time. Surviving this disease gave me a terrible responsibility to talk about it almost every day for the last 11 years. To relive the panic, the debridements, skin grafts, the amputations, the emotion anguish of watching my body disintegrate at age 22. You can help me with this responsibility. You can put this vaccine in every health insurance plan and every pediatrician's office in America. Please, don't let me down. I believe this is why I went through that pain. I went through all of that so that I could be here today in front of you pleading for you to help me make sure others don't go through it. Please, don't let me down.

Dr. Leah Luckeroth
Andy Marso's Initial Physician

That's a hard act to follow. Greetings from Kansas. I'm Dr. Leah Luckeroth. I am here speaking on my own behalf as a mother, friend, and a physician. I have absolutely no conflicts. Eleven years ago, Andy Marso presented to Watkins Health Services at the University of Kansas carried in by two of his friends due to extreme pain in his extremities. I was getting ready to leave the building for lunch when I received a call from one of our nurses concerned about a student who had just arrived. I walked into the treatment clinic and knew immediately that this was an emergency when I saw the dusky, cyanotic color of Andy's skin. I placed my hand on his forearm, seeing for the first time the rash of meningococcemia. It was more frightening than the pictures I had seen in textbooks. Andy, who was a National Merit Scholar and on track to graduate number one in his class in the School of Journalism in May, was still coherent and answered my questions as I asked the nurse to call 911. In less than 10 minutes, the ambulance had arrived. One physician was talking to Andy's friend Clay about close contacts, another physician was talking to Andy's father in Minnesota, and I had reviewed his case with the Infectious Disease Specialist at our local hospital. Time was of the essence. This deadly disease strikes without warning. I can remember taking my dose of Cipro and trembling as I felt that Andy would not survive the night. I hugged my two daughters closely that evening, realizing with a jolt of reality that this student could've easily been my child. Over the ensuing hours and days, there would be meetings at Andy's scholarship hall where he lived, with the campus newspaper students that he worked with on a daily basis, his soccer buddies, and an e-mail would be sent campus-wide from the Chancellor. The university would later adopt a policy mandating the meningococcal ACYW vaccine for all students living on campus. Andy lost most of his fingers and part of his feet, but stands tall today as a miracle and advocate for the prevention of meningitis. He continues to educate medical professionals and the public about the disease. Now that more people than ever have viable health insurance that puts prevention first, we have the opportunity to save lives with a simple vaccine. This past week, my daughter received her first dose of the meningitis B vaccine before she travels to college in August. Eleven years later, I felt that jolt of reality knowing how fortunate my daughter was to have this option that did not exist for Andy. Please do the right thing and approve this vaccination for prevention of meningitis in all adolescents and college students and everyone else. There is no dollar amount that could ever replace Andy or any student. Prevention and education are the key factors to lowering the cost of healthcare. I agree with what Andy said. I don't have a business degree, but if it only costs $50 in Europe and it costs $400 here, certainly we can get

an MBA to help us with the price. I am thankful to be here today as an advocate for meningitis B prevention and as part of Andy's amazing life story. Thank you.

Mara Berger
Mother of Adam Berger

Mara Berger from Chicago, Illinois. I don't have any affiliation yet, but I'm a grieving mother. In 2005 the FDA licensed and approved the conjugate Menactra® for routine use in 9 months to 55-year-olds. The FDA said after thorough research that the vaccine is effective, safe, and immunogenic. However, at that time, your predecessors of the ACIP committee didn't recommend the vaccine for the FDA's approval. Instead, the ACIP prioritized and gave the vaccine approval and recommendation for adolescents only. To date, there is still no recommendation for 9-month-olds to 55-year-olds. Now the CDC does take care of the children and young adults and adolescents, but what about the adults 21 to 55 who die or get maimed from this insidious disease? The Strain C with sepsis, *Neisseria meningitis* C and septicemia. CDC does not recommend the vaccine to healthy adults in their literature. My son, Adam, was a beautiful human being. I took him into an emergency room thinking he had the flu. I've read this so many times on the Internet. Emergency room doctors must be retrained and the nurses. They know nothing about meningococcal disease. Everything they do, they only focus on the flu. We went in the morning. He had a 104^0 fever. They told us it was the flu. We went home, and when we returned, he had the most virulent headache. The triage nurse told us to go home, that it was flu, and there was nothing they could do. I threw a big stink. They were mad at me because I wouldn't stop saying, "We're staying. I don't care what you say. We're staying." They made my son wait five hours in the emergency room where he could have infected everyone because he was so contagious. When he was finally seen, they gave him the antibiotic because he had septicemia. Now I did not know—I had heard of meningitis, but I really did not know anything about meningococcal disease. Well, I studied it and researched it. I would challenge any infectious disease doctor here on my knowledge versus theirs.

I can't believe that for 10 years this vaccine has been approved by the FDA and the ACIP committee has not recommended the vaccine. Do you think that healthy adults don't get this disease? It's the healthy people that get the disease, because they don't have enough antibodies to protect them, plus he was a nursing student at a prestigious private hospital. He thought he got the recommended vaccines. Come to find out, after his death, he didn't get a meningitis vaccine because the private hospital follows the CDC's recommendations that only epidemiologists should get the vaccine. Aren't hospitals full of bacteria? Sick patients come in with meningococcal disease. Do you know how many firemen, emergency staff, paramedics have gotten the disease from a patient they've transported to hospitals? I believe that adults 21 to 55 are at most risk. A friend of mine, she's 50 years old, she went to her doctor. She said, "Do I need a meningitis vaccine?" "Oh, no. You don't live in a dorm." That's the mindset of many doctors. Since the vaccine is not recommended for adults, doctors don't keep up on the information about meningococcal disease. They talk foolish. I can go into Walgreens right now and get Menactra® shot. I don't have to ask anybody. As long as the FDA approved it and licensed it, we really don't need your recommendation. The only way we need your recommendation is so that the insurance companies pay for the vaccine. I'm lucky. I have Blue Cross/Blue Shield and they pay for the vaccine whether you recommend it or not. But in the meantime, people are dying. The ACIP committee has an obligation to stop the disease at any cost. Controlling outbreaks is not eradication. The only eradication is vaccine. You have to educate the public from preschool to grad school—the parents, the children, the nursing staff, the colleges. Anyone should be able to get this vaccine, even staff at schools. Recommend it routinely the way the FDA intended 10 years ago. There have been thousands of maimings

and deaths, and you've turned a blind eye. I don't get it. I implore you that the ACIP and the CDC have to come together and approve this Menactra® for the ACWY-135 as soon as possible. This disease is not rare. It's sporadic. All over the country. One here. Two there. Please act accordingly and responsibly. Thank you.

Dr. Deborah Wexler
Executive Director
Immunization Action Coalition

I'm Dr. Deborah Wexler, Executive Director of the Immunization Action Coalition (IAC). IAC is proud to receive funding from CDC, almost all vaccine companies, individuals, coalitions, and more. I'm here today because I have attended ACIP meetings for more than 15 years and have witnessed hours of discussion as the committee strives to determine the right thing to do in protecting the health of the nation. It is within this context that I offer the following reasons for you to support a routine recommendation for MenB vaccine. First, for simplicity and clarity. ACIP has recommended the use of meningococcal vaccine against Serotypes ACWY for 10 years. How can we justify doing less for serogroup B? In addition, having a routine recommendation for one meningococcal vaccine and a permissive recommendation for the other is unnecessarily confusing for both parents and providers. Parents may erroneously think that their vaccinated children are protected from Meningitis when in reality, they have been vaccinated against only ACWY. A routine recommendation for MenB would be simpler to follow and would alleviate confusion for everyone concerned. Second, it was my understanding that insurance is unlikely to pay for a vaccine which lacks a routine ACIP recommendation, which would create a two-tiered approach to disease prevention. I've learned here today that, perhaps, VFC would cover this vaccine if it were a permissive recommendation. But, it still concerns me that private insurance and HMOs may not cover the vaccine because it's a permissive recommendation. If it's not on the CDC immunization schedule, the vaccine may not even be discussed unless a knowledgeable parent brings it up. Third is cost, and the people here who have spoken before me have been so eloquent on this topic. Ironically, cost is a consideration both in support of and in opposition to a routine recommendation. ACIP tends to focus on the high cost of the vaccine per case prevented. But, what about the cost to a parent whose child has died from a preventable disease? And what is the cost to a young adult of having one or more limbs amputated or having other lifelong disabilities from a preventable disease? And what are the costs, both in dollars and the emotional toll, for colleges and communities dealing with an outbreak of a preventable disease? These concepts must also be factored into any discussion of cost. As public health professionals, we are all dedicated to prevention. I know that you as ACIP members are charged with making recommendations that balance difficult and seemingly competing objectives. But to me, the answer is clear. I choose prevention, and I ask you to choose a routine recommendation to protect all teens with MenB vaccine. You have the power to prevent a deadly and devastating disease that can have an overwhelming impact on young people and all the people who love them, as we have just heard. A routine recommendation is quite simply the right thing to do. Thank you.

Kamay Lafalaise
National Consumers League

First, I'd like to take a moment to share my deepest respects and condolences for the families and the survivors that have shared their stories with us today. So, thank you. Good morning, everyone. My name is Kamay Lafalaise, representing the National Consumers League (NCL), and I have no conflicts of interest to declare. Based in Washington DC, the National Consumers League is the nation's oldest consumer advocacy organization, founded in 1899, and provides the consumer perspective on matters that affect consumers, including health-related issues. In February, the National Consumers League Executive Director, Sally Greenberg, stood before this committee urging it to add serogroup B meningococcal, or MenB, vaccines to the routine schedule of vaccines. We are here today to echo that same message before more lives are needlessly lost to this devastating disease. Making safe and effective medications and healthcare widely available to all Americans has been a long-standing priority to NCL. We recently conducted a survey of parents to explore attitudes, behaviors, and misconceptions regarding vaccines. Among other things, we found five significant points that I'll share with you today. First, the majority of adults, 87%, support mandatory vaccinations for school-aged children. Second, 81% of parents find healthcare providers to be a trusted source of vaccine information. Third, about 30% of parents still believe that vaccinations can cause autism, which demonstrates the critical need to educate the public and strengthen our message. Fourth, 84% of parents cite protecting a child from disease as the top reason to vaccinate, followed by protecting family from disease, helping to eliminate the disease, and lastly, protecting the community from disease. Fifth and finally, of all childhood diseases, parents are most concerned about meningitis. Not only do these findings highlight that there is an ongoing need for vaccine education, but that Americans see vaccines as a way to protect our children and community from disease, and they take very seriously the threat of meningitis. A routine or Category A recommendation for the MenB vaccines would allow for patient education about the disease, and the availability of this new vaccine before an outbreak occurs. Because of the highly contagious nature of the disease and its debilitating effects, including loss of limbs and death, the vaccine to prevent MenB would be available to all parents and children, not just those who are aware of the vaccine and specifically request it or those who can pay out-of-pocket costs. You have heard powerful testimony today from several people afflicted by this frightening disease. If we wait, it could be too late. How many lives need to be lost before we take preventative action? We see no reason to expose anyone to this terrible illness when complete protection and prevention is available. Once again, NCL believes that parents and young people should have access to these two FDA-approved vaccinations *before* a deadly outbreak occurs and, therefore, both vaccines should be added to the routine schedule. Thank you very much.

Neal Raisman
Father of Isaac Raisman
Spokesperson, Global Healthy Living Foundation

Good morning. My name is Neal Raisman. In 2005, I was the father of two. Today, I am the father of one. On the morning of September 27th, my youngest, my son Isaac, woke with a headache and was dead of meningitis by 4:30 the same day. I found his body. He had died less than 12 hours from the time he had told us he had a headache until he died. A vaccine would have prevented his death. It's an epidemiological story you all know too well, but it's a personal story I never wanted to know. Today, I'm here as a spokesperson for the Global Healthy Living Foundation. Together we're asking this committee to endorse the FDA labeling recommendation for broad immunization to prevent the invasive disease, death, and physical devastation caused by meningitis serogroup B, especially for individuals 10 through 25 years of age. My appearance here today in your committee meeting could not come at a more immediate time. Lauren Jones at the University of Oregon added her name to the list of those who have died of meningitis. A UC Davis student was also diagnosed in February, and others in Tennessee, Washington DC, and Rhode Island. These schools now see the need for a vaccine to be available to all of their students, not just the ones who can afford it. Since the FDA approved the vaccine for meningitis strain B in November 2014, there have been over 50 cases of meningitis strain B. Did they get infected because the ACIP didn't act to make the vaccine available to all? Perhaps. Although the vaccine was available to those who could afford to pay for it, without your recommendation, as you know, insurance companies and Medicaid won't cover the costs. It's not difficult to conclude that informed people with the money to pay for the vaccine have lived and those who can't afford it or don't even know about it have been infected. This is counter to everything the ACIP, the CDC, the FDA, and the NIH stand for. Your endorsement vote for the FDA recommendation would realign this committee with its mission, with the values and expectations of parents with college-aged children. We expect the government to tell us when the health of our children is in danger, and then help us decide what to do. Because meningitis is nearly always fatal or at least physically devastating, the low number of people affected masks the toll these cases take on families such as mine and on communities. My job today is to help you understand the depth of the emptiness we parents feel every day and the heartache we feel for those parents who are about to join our ranks—the ranks of families minus one. Please act so other young people and their families are not so violently affected by meningitis. Let there not be another Lauren Jones or an Isaac Raisman, my son who died of meningococcal. You can do this, and I urge you to do so today. As for cost-benefit analysis, what is the cost of a life and what is the benefit of an early death?

Dr. Temte thanked all of the public commenters for sharing what must be very difficult stories, and expressed ACIP's appreciation for their heartfelt and very thoughtful comments.

Proposed Recommendation

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. MacNeil showed and read through the WG's proposed recommendation language for use of MenB vaccines in adolescents:

> "A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. (Category B)"

In addition, the following language would be provided as guidance for use:

- MenB should be administered as either a 2-dose series of MenB-4C or a 3-dose series of MenB-FHbp
- The same vaccine product should be used for all doses
- Based on available data and expert opinion, MenB-4C and MenB-FHbp may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible
- No product preference to be stated

Discussion Points

Dr. Temte asked whether this would appear on the schedule or whether the WG had considered this.

Ms. MacNeil indicated that this had not been discussed specifically, but she thought the WG would be open to having a line in the schedule for the vaccine, with footnotes to explain it further.

Dr. Vazquez said that to be clear, as a pediatrician who attends clinics, there is a difference in having a vaccine on the schedule versus on the table. It is very important for practitioners trying to figure out how to counsel their patients and parents that there is agreement. If the vote is for a Category B recommendation, she thought that the MenB vaccines should appear on the table and not solely in the footnotes.

Ms. MacNeil said that they could work with the Childhood Schedule WG to put that on the schedule for next year.

Dr. Romero added that as the Chair of the Childhood Schedule WG, he will make sure that they have very strong discussions about including these on the schedules—on the table, not just as a footnote.

Dr. Loehr (AAFP) pointed out that the schedules have certain colors, none of which match this recommendation. The current colors are for "recommended for all children," "catch-up immunization," or "certain high-risk groups." A new color would be needed for this recommendation.

Dr. Schuchat reminded everyone that there have been other options over the years, and the schedule is voted on every year. In 2009, there was an equivalent of a Category B for HPV vaccine for boys in the period before there were additional data on the outcomes, at which time it became a Category A. It was on the schedule with a hatched-mark, not a footnote. The schedule committee will look at that option for this year's schedule, and that will come back to the full ACIP in October 2015 for vote.

Dr. Reingold had two different immunization schedules, one of which went through age 18 and the other which started at age 19. He presumed this would have to appear on both.

Ms. MacNeil confirmed that it would.

Given the uncertainty regarding duration of protection, Dr. Harrison wondered why "short-term" protection was specified.

Ms. MacNeil replied that the WG's rationale for adding that language was to ensure that people are aware that prevention may not be long-term and that these vaccines will not prevent all cases.

Dr. Belongia thanked all of the survivors and family members for sharing their stories. He said that his hesitation at the moment regarding the Category A, which he could easily endorse, pertained to safety concerns, not cost-effectiveness. He wondered if it would be helpful to add some language to the recommendation indicating that the committee will reevaluate the potential to make a Category A recommendation when additional safety and effectiveness data become available.

Dr. Temte reminded everyone that for the Tdap recommendation for pregnancy, ACIP specified that the safety aspects would be paramount to that recommendation and requested that ongoing safety studies be performed.

Dr. Harriman emphasized that the vaccine would be covered under the VFC program, and that insurance companies would be compelled to pay with a Category B recommendation.

Dr. Netoskie (AHIP) commented that AHIP values vaccines and recognizes that they offer great value. Many health plans are already covering this vaccine. AHIP also wants to ensure that as determinations are made through ACIP, it is important to understand ACIP's view of vaccine effectiveness, cost, and safety. Health plans will cover A and B recommendations when provided in-network. Also, grandfathered plans would be exempt from this mandate. There are also post-approval timelines following publication in *MMWR*. There would be some varied uptake with plans over the course of the following year. Uptake in physicians' offices would probably also vary depending up their views of the vaccine. He would say that health plans tend to be more proactive regarding promotion of Category A recommendations based on appropriate age, risk, et cetera. Vaccines with Category B recommendations, permissive, are somewhat difficult to promote broadly in the plans, whether promoting to clinicians or patients who may have gaps in care based on appropriate age or vaccine need.

Dr. Kempe emphasized that it is extremely important to collect data about safety, efficacy, and carriage. This is clearly important to incorporate into guidelines.

Dr. Bennett thought they could feel confident this would occur. This is similar to the recommendation for pneumococcal vaccine in those over the age of 65. There are a number of studies going forward to try to address the effectiveness of that recommendation, and she thought this was the same type of situation. While she did not believe they actually incorporated that into the recommendation, there was discussion.

Ms. Pellegrini stressed that members considering support of a Category B recommendation were not doing so because they were wildly enthusiastic that it would be exactly the right recommendation long-term for this vaccine. There simply was not adequate information at this point to support a Category A recommendation. In that context, she urged the manufacturers to provide those data as quickly as possible. She also encouraged CDC to determine how to increase reporting to better understand the burden—not just the numbers of cases and the numbers of deaths. It is important to understand the long-term consequences and the cost of medical expenses to survivors and families out-of-pocket. Survivors are dealing with profound lifelong consequences, which should be factored in. If a Category B recommendation was made, she thought this offered a golden opportunity for CDC to study the policy impacts with regard to whether providers carry the vaccine and how patients take it up. This could provide an incredibly useful case study for the future and for understanding the impact of the recommendation ACIP makes. She looked forward to the vote during this session, as well as revisiting it in the near future.

With all due respect, Dr. Reingold submitted that this is one of the diseases for which the burden of disease is known as meningitis is one of the better reported diseases in the US. The ABCs data are very compelling and are extrapolatable to the rest of the country. He does think more effectiveness and safety data are needed.

Dr. Even (ACHA) reiterated that ACHA understands the devastating burden of the disease. They are highly committed to education about vaccines in general, as well as the booster dose that is needed for the quadrivalent meningitis vaccine. They are pleased to have reached a point of making some recommendations, which offers a springboard before the fall semester.

Vote: Use of Serogroup B Meningococcal Vaccines (MenB) in Adolescents and Young Adults

Dr. Campos-Outcalt made a motion to accept the wording as stated for the use of serogroup B vaccines in adolescents and young adults. Dr. Rubin seconded the motion. The motion carried with 14 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
1 Opposed:	Harrison
0 Abstained:	N/A

Vaccines for Children

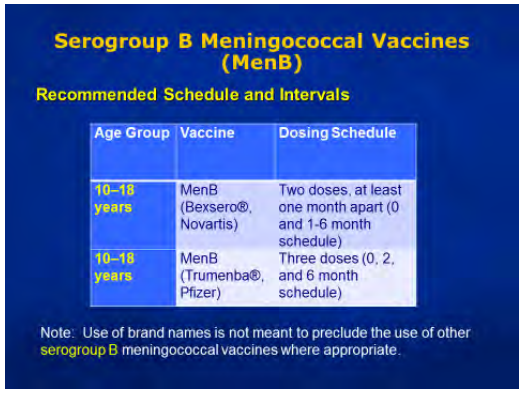
Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli indicated that the purpose of this revision was to update the resolution to allow individual clinical decision-making regarding the use of serogroup B Meningococcal vaccines in children aged 16 through 18 years. She reminded everyone that this resolution had two parts. The first regarded meningococcal conjugate vaccines, while the second pertained to serogroup B meningococcal vaccines. There were no proposed changes to the Meningococcal Conjugate Vaccine section of the resolution. For the section regarding serogroup B Meningococcal vaccines, the proposed changes are underlined:

Eligible Groups

- Children aged 10 through 18 years at increased risk for meningococcal disease attributable to serogroup B, including:
  - Children who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5-C9, properdin, factor H, or factor D or taking eculizumab [Soliris®])
  - Children who have anatomic or functional asplenia, including sickle cell disease
  - Children identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroup B
- Children aged 16 through18 years without high risk conditions may also be vaccinated

In the section on recommended schedule and intervals, the table was updated to remove specific information that indicated this is for high-risk use and a correction was added in the footnote. There were no changes to the recommended dosing schedule:



No changes were made to contraindications and precautions, which can be found in the package inserts available at:

http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

No changes were proposed to the statement regarding updates based on published documents:

> [If an ACIP recommendation regarding meningococcal vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL].

Vote: VFC Resolution for Use of Serogroup B Meningococcal Vaccines (MenB) in Adolescents and Young Adults

Dr. Romero made a motion to approve the VFC MenB vaccines recommendation for adolescents and young adults. Dr. Bocchini seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

General Recommendations

Introduction

Dr. Marietta Vázquez
Chair, General Recommendations Work Group

Dr. Vázquez reminded everyone that the General Recommendations document is published in the *Morbidity and Mortality Weekly Report* (*MMWR*) every 3 to 5 years, and addresses a broad range of clinical practice issues that are relevant to all vaccines as opposed to the vaccine-specific publications. The General Recommendations are intended to address topics that cannot be attributed to a single vaccine, but that are germane to the practice of immunization in general. A number of topics have been or are being revised, including the following:

- ❑ Timing and Spacing of Immunobiologics
- ❑ Contraindications and Precautions
- ❑ Preventing and Managing Adverse Reactions
- ❑ Reporting Adverse Events After Vaccination
- ❑ Vaccine Administration
- ❑ Storage and Handling of Immunobiologics
- ❑ Altered Immunocompetence
- ❑ Special Situations
- ❑ Vaccination Records
- ❑ Vaccination Programs
- ❑ Vaccine Information Sources

During this session, a vote was planned for the second half of the document to include the following topics:

- ❑ Altered immunocompetence
- ❑ Special situations
- ❑ Vaccination records
- ❑ Vaccination programs
- ❑ Vaccine information sources

Content already reviewed and discussed by ACIP include:

- ❑ Altered immunocompetence (June 25, 2014)
- ❑ Special situations (February 20, 2013)
- ❑ Vaccination records (October 23, 2013)
- ❑ Vaccination programs (June 25, 2014)
- ❑ Vaccine information sources (October 29, 2014)

A vote is necessary for CDC clearance and publication. The presentations during this session pertained to changes that have occurred since ACIP last discussed the document; special situations, including updates related to ACIP vaccine-specific statements; and major revisions in three sections: Altered Immunocompetence, Vaccination Records, and Vaccination Programs. Dr. Raymond Strikas presented on behalf of Dr. Andrew Kroger who was unable to attend.

Dr. Vázquez thanked ACIP for the opportunity to serve over the last four years; Dr. Kroger, the CDC lead, who is one of the most organized and detailed-oriented persons she has ever had the pleasure to work with; and the WG in general.

General Recommendations: Final Five Sections

Raymond Strikas, MD, MPH, Medical Officer
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Strikas thanked ACIP for the opportunity to present revisions to the General Recommendations on Immunization, and Dr. Andrew Kroger for leading the Working Group with Dr. Vazquez. He indicated that ACIP members had drafts in front of them in both track changes copies and clean copies. He frequently referred to page numbers and line numbers in this presentation, and these numbers corresponded to the track changes version of the document.

Regarding the Altered Immunocompetence section, many of the changes were already presented to ACIP in June 2014 for which Dr. Strikas shared background information. The 2011 General Recommendations currently contains a section on Altered Immunocompetence. The source for revised content to this section comes from the cleared ACIP *MMWR* vaccine-specific statements, and the Infectious Diseases Society of America's (IDSA's) position statement on this topic. The full citation for the IDSA document, on which ACIP member Lorry Rubin is first author, is as follows:

> Rubin, LG, Levin MJ, Ljungman P., et. Al. 2013 IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host. Clin. Infect. Dis. 2014; 58: e-44-100.

This is an evidence-based set of guidelines that involved multiple stakeholders in its development. Prior to publication, CDC was asked to comment on potential areas that might represent a deviation from the ACIP vaccine-specific statements. The IDSA's publication, entitled *Clinical Practice Guideline for Vaccination of the Immunocompromised Host*, expands greatly upon the content in the 2011 General Recommendations on Immunization, which is why the General Recommendation's WG incorporated as much as possible into the revised General Recommendations and the vaccine-specific statements. There are some minor areas of difference between this document and the vaccine-specific statements. The major goal of the WG has been to distinguish those topics which are "General" in nature, and to stay away from vaccine-specific recommendations because of the risk that they might not match ACIP statements exactly. However, there are relatively few such differences.

The revisions to the Altered Immunocompetence section include four major topic revisions and source material. First, the IDSA identified some new conditions and some new medications under the classification of altered immunocompetence, so these were added to the General Recommendations. Second, those who were present during the June 2015 meeting may recall that a major change in the tenor of discussion was the added weight given to the issue of vaccine effectiveness. This is described in detail in the IDSA document, and is an issue that applies to both live and inactivated vaccines. It involves the complex issue of potentially withholding a vaccine if the condition or the medication is present, and if the vaccine is withheld, at what interval it is considered safe and effective to give the vaccine after the altered immunocompetence is no longer present. Third, the General Recommendations have been updated to discuss altered immunocompetence as an indication to vaccinate outside of the routinely recommended ages, and relies exclusively on CDC vaccine-specific statements. Fourth, the discussion of vaccination following hematopoietic cell transplants (HCT) has been updated, using evidence from the IDSA document primarily, but also relying on some CDC vaccine-specific statements as well.

Here are some of the new additions to the list of conditions and medications that are described in the General Recommendations:

- Conditions
  - Interferon gamma/interleukin 12 axis deficiency
  - Interferon alpha deficiency
  - Interferon gamma deficiency
  - Phagocyte function disorders (e.g., Chediak-Higashi syndrome)

- Medications
  - Induction/consolidation chemotherapy
  - Anti-B cell antibodies (example rituximab)

- Combination Medication/Conditions
  - Patients with major antibody deficiencies receiving immunoglobulins

These are specific categories defined in the IDSA guidelines, and have relevance because of changes to the current general recommendations. This section contains language that allows physician discretion in the determination of whether any of these conditions are present.

Some of the new recommendations relevant to these conditions reflect categories of vaccines that can either be administered or withheld. In most cases, this information is presented in a table on Page 13 of the marked up version. Certain conditions require only the withholding of live bacterial vaccines, not live viral vaccines. This includes interferon gamma/interleukin 12 axis deficiencies. But there are also recommendations to withhold both live viral and bacterial vaccines in patients with interferon alpha deficiency and interferon gamma deficiency. Teasing out the different pathways of these interferons will be the job the of the immunologist or other specialty physicians, which is why it is critical that providers using the General Recommendations be provided with opt out language for referral to these specialists. For other conditions, the General Recommendations borrow some of the specific rationale for withholding of live vaccines. For instance, patients with leukocyte adhesion defects, myeloperoxidase deficiency, and Chediak-Higashi syndrome have specific deficits in T-cells and natural killer cells that render a reduced immune response to live viral and live bacterial vaccines, which is why both categories of live vaccines are to be withheld for such patients. For other phagocyte deficiency disorders, such as chronic granulomatous disease, these cell lines are not deficient so withholding is restricted to live bacterial vaccines.

IDSA also invoked some of these conditions in the context not only concerns with safety and effectiveness of live vaccines, but also the effectiveness of inactivated vaccines. Conditions in which IDSA supports withholding both categories of vaccines include induction/consolidation chemotherapy (Table Footnote, Page 15) and patients with major antibody deficiencies receiving immunoglobulins (Table Footnote, Page 15). IDSA also defines a category of conditions as “high-level immunosuppression” including cancer chemotherapy (P5, L6), radiation therapy (P5, L6), solid organ transplantation (P11, L13), human immunodeficiency virus (HIV) with immunosuppressive parameters defined (P6, L22), patients receiving high-dose immunosuppressive corticosteroid therapy (P10, L33), and patients receiving biologic immune modulators (P11, L36). The page and line numbers represent the location in the General Recommendations where these medications are described.

Incorporating IDSA recommendations occurred against a backdrop of what is currently described in the 2011 General Recommendations. The General Recommendations already had an extensive discussion of intervals. In terms of the specific intervals that are proposed based on integrating General Recommendations with IDSA recommendations, for those types of conditions/medications labeled “high-level immunosuppression,” IDSA harmonized with 2011 General Recommendations in recommending a 3-month interval from medication to vaccine, at least with respect to cancer chemotherapy and inferred high-level steroid use as well (P5, L10). There is a vaccine-specific exception of a 1-month interval between certain categories of high-level immunosuppression, notably zoster vaccine, in which a 1-month interval has been established by ACIP vaccine-specific statement. These intervals vary by direction: when a live vaccine is given first, IDSA recommends a 1-month interval from the live vaccine to the medicine or condition, and for inactivated vaccines there is a 1-month preference but a 2-weeks recommendation from inactivated vaccine to medicine (P5, L8). IDSA has introduced exceptions to the 3-month rule when medicine is given first. For Anti-B cell antibody therapy, the interval should be 6 months (P5, L15). For solid organ transplant rejection therapy, the evidence supports a range of 2 to 6 months for an interval, which practically could be considered a 2-month interval (P11, L32). IDSA also defines a category of immunosuppression defined as “low-level immunosuppression.” Examples are lower doses of corticosteroids; alternate day corticosteroids; and the examples set out in the ACIP zoster-statement with defined doses of azathioprine, methotrexate, and 6-mercaptopurine.

The discussion of intervals and withholding vaccines is woven into the text of the new draft with General Principles (Beginning P4, L44). Live vaccines effectiveness concerns and safety concerns are both relevant, with primacy given to safety. With inactivated vaccines there are safety concerns and effectiveness concerns, with effectiveness being the primary rationale for withholding. Inactivated influenza vaccine is an exception to the withholding rule, but the dose should be repeated if given when the patient is no longer immunocompromised (Table, P15). The topic of altered immunocompetence as an indication to give a vaccine outside of routinely recommended ages (P2, L13) is less complex because it involves simply updating the General Recommendations with content from vaccine-specific statements. The changes are highlighted on Page 2 beginning with Line 13, and apply primarily to the bacterial vaccines Hib, meningococcal conjugate vaccine, and pneumococcal vaccines. These recommendations are primarily driven by rare conditions like asplenia and complement component deficiency. The meningococcal vaccine languages requires modification here to be consistent with ACIP's prior recommendations.

Patients who have received an HCT (hematopoietic cell transplant, bone marrow transplant, or umbilical cord stem cell transplant) require special consideration because not only do they have altered immunocompetence, but also their treatment wipes out their entire immune system, also called immunoablation. This treatment removes immune cell memory. Therefore, these patients eventually require revaccination with a complete or near complete primary series of all vaccines received previous to the transplant. Specific regimens were described in the journal *Biology of Blood and Marrow Transplant* in 2009 [Tomblyn M, Chiller T, Einsele H, Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective Biol Blood Marrow Transplant 15: 1143-1238 (2009) 2009 American Society for Blood and Marrow Transplantation]. The 2011 General Recommendations borrowed content from this journal and cited it heavily in the General Recommendations. CDC also placed the article on its website for reference. Reliance on this source document was vetted through ACIP during the presentations that led up to the 2011 iteration of the General Recommendations. The IDSA provides detailed recommendations for vaccination of HCT recipients in their 2013 document, and the lead author of the 2009 blood marrow paper is an author on the IDSA document as well.

Revaccination with the following vaccines is recommended post-hematopoietic cell transplant: DTaP, PCV13, PPSV23, Hib, HepA, HepB, meningococcal vaccines, IPV, IIV, HPV, Varicella, and MMR. Revaccination is not recommended with BCG, LAIV, typhoid vaccine, rotavirus vaccine, and zoster vaccine. The interval following the HCT and beginning the revaccination series varies depending upon whether the vaccine is inactivated or live. The interval for inactivated vaccines is 3 to 6 months. Most are 6 months, though pneumococcal vaccine is specified as 3 months. For live vaccines, the interval is 24 months and the responsible physician should be sure the patient is immunocompetent and does not have chronic graft versus host disease. The guidance in the IDSA recommendations address revaccination doses following HCT. However, there is little discussion about first-time vaccination following HCT; that is, administration of doses that have not been given before the hematopoietic cell transplant. CDC does have specific guidance for some vaccines. Some of this guidance is unpublished such as for zoster vaccine, Tdap vaccine, and Hib vaccine. For zoster vaccine, IDSA says vaccination is not recommended because the vaccine that should be administered is varicella vaccine post- HCT, presuming that VZV immunity is ablated. Unpublished CDC guidance for zoster vaccine is that it can be administered following risk-benefit analysis. There is the possibility that someone post- HCT will be exposed to varicella disease and then become a candidate for zoster vaccine. Personal communications with pertussis subject matter experts (SMEs) at CDC state that if pertussis-containing vaccination is not documented prior to the

transplant, then post- HCT vaccination recommendations should consist of routine vaccination based on age. Finally, revaccination with three doses of Hib vaccine are recommended by CDC regardless of Hib vaccination prior to hematopoietic cell transplant. This is in the Hib-specific ACIP statement.

Some sections from the draft are unchanged from the 2011 General Recommendations. One of the most important is that the level of immunocompetence should be determined by a physician. The General Recommendations identifies certain categories and laboratory tests, but this is not meant to be all-inclusive. There is a section on Vaccination of Household Contacts of Immunosuppressed Persons. Some language was added on the length of time for rotavirus vaccine virus shedding. Clarification was added regarding the definition of a "protected environment" with respect to health-care providers to determine whether they should preferentially receive IIV as opposed to LAIV. Otherwise, the language in this section provides a strong recommendation to vaccinate household contacts of persons with altered immunocompetence, and this language is harmonious with that in the IDSA document.

The major changes to the Special Situations section of the General Recommendations, none of which is new since the content was presented to ACIP in February 2013, is language stating an exception to vaccination of breastfeeding women. Breastfeeding is considered a precaution for Yellow Fever (YF) vaccine since there have been cases of apparent vaccine-derived disease in breastfeeding infants who were not vaccinated themselves but whose mothers were (P6, L 33). Also, the Vaccination in Pregnancy section is now harmonized with Tdap ACIP vaccine-specific recommendations (P7, L 29). The language from the 2011 document was kept regarding a physician's decision to vaccinate by the intramuscular (IM) route for patients with bleeding disorders. They can choose to do this if the bleeding risk is acceptable.

Changes to the General Recommendations in the section on Vaccination Records were presented to the ACIP in October of 2013. These changes describe the increasing capacity of vaccination registries, also known as Immunization Information Systems (IIS). As described in the draft, capabilities of an operational IIS are as follows (P2, L26):

> "A fully operational IIS also can prevent duplicate vaccinations, forecast when the next dose is due, limit missed appointments, allow recall for those who missed appointments, determine when vaccines need to be repeated (evaluation), reduce vaccine waste, and reduce staff time required to produce or locate vaccination records or certificates."

There also is a reference to Meaningful Use integration (P2, L36), defined as the capacity of an IIS to integrate its functionality with other electronic health records (EHRs). Language from CDC's web site is placed into the General Recommendations:

> "Electronic health records should maintain interoperability with IIS's as part of an effort to improve the quality of care, reduce health disparities, engage patients and families in their health, improve the security protection for personal health information (REFERENCE www.cdc.gov/ehrmeaningfuluse/introduction.html").

The Vaccination Programs section of the General Recommendations outlines programmatic aspects of immunization. New additions to this section of the document include the addition of language from the National Vaccine Adult Standards (P1, L6) stating:

> "All healthcare providers, whether they provide immunizations or not, should incorporate immunization needs assessment into every clinical encounter, strongly recommend needed vaccine(s) and either administer vaccine(s) or refer patients to a provider who can immunize, stay up-to-date on, and educate patients about vaccine recommendations, implement systems to incorporate vaccine assessment into routine clinical care, and understand how to access immunization information systems (i.e. immunization registries)."

The Vaccination Programs section is divided into a discussion of child immunization, adolescent immunization, and adult immunization. No major revisions have been made to the section on child immunization or adolescent immunization. However, language has been included in the adult immunization section related to the Affordable Care Act (ACA). The language in the draft reads:

> "Effective for private health insurance plans drafted or updated after September 2010, coverage for ACIP recommended vaccines must be covered without deductibles or co-pays, when delivered by an in-network provider." (P10, L7)

Since the draft was developed, official language related to the ACA has been changed, so the internal CDC preference was to change the language to read:

> "The Affordable Care Act (ACA) requires insurance companies to cover all immunizations that are included on the immunization schedule with no copay and no deductible."

This new language emphasizes the role of the Child and Adult Schedules for defining immunization coverage. It also does not emphasize the fact that some insurance companies are grandfathered out. The new language does not emphasize "private" insurance companies, although Medicare is subject to additional regulation that might not be completely harmonized with ACA.

In terms of Vaccination Information Sources, the following is a listing of organizations and projects related to immunization in the US:

- CDC-INFO Contact Center
- National Center for Immunization and Respiratory Diseases (NCIRD)
- American Academy of Pediatrics (AAP)
- American Academy of Family Physicians (AAFP)
- American College of Physicians (ACP) (new)
- American Congress of Obstetricians and Gynecologists (ACOG) (new)
- Immunization Action Coalition (IAC)
- Vaccine Education Center (VEC), at the Children's Hospital of Philadelphia
- Institute for Vaccine Safety (IVS)
- Group on Immunization Education–Society for Teachers of Family Medicine (GIE-STFM)
- State and Local Health Departments

A URL and short description of activities are listed for each of these groups. The National Network for Immunization Information was removed, which was formerly an affiliate of IDSA, AAP, AAFP, PIDS, American Nurses Association (ANA), National Association of Pediatric Nurse Practitioners, ACOG, University of Texas Medical Branch, Society for Adolescent Medicine, and the American Medical Association (AMA). The National Network for Immunization Information is currently under new direction, and it is unclear which organization is the parent organization.

Discussion Points

Dr. Temte indicated that members were missing a document, but had seen it prior to the February 2015 ACIP meeting and it was made available electronically as well.

Dr. Kempe proposed a brief addition. Her group has conducted several surveys recently showing the knowledge about IISs, particularly among adult providers, is negligible. She wondered whether, under capabilities of operational IISs, there could simply be a statement made that all states have either regional or state IISs.

Dr. Strikas indicated that this was fine with him, but pointed out that the committee should weigh in.

With the mobility of the population, Dr. Dwelle (ASTHO) was concerned with the interstate and interoperability of IISs. He wondered whether that was discussed and if recommendations were made about this in the document.

Dr. Strikas indicated that it is alluded to, but is not discussed in detail.

Dr. Moore (AIM) thought the CDC recommendation to remove the reference to in-network providers and simplify the statement on coverage may prove to be more confusing than helpful to readers. From an operational standpoint in dealing with people looking for coverage for their vaccines, the fact that the coverage that is required is through in-network providers is critically important. Many local health departments are not yet in-network providers. When an uninsured person presents to a health department, they have to be charged for vaccines or be told to go elsewhere to receive them. She urged the inclusion of the in-network provider clause to prevent confusion.

Referring to Slide 23, Dr. Strikas said that the rationale for inclusion of the second bullet was that it was simpler. If he understood the comment, Dr. Moore was favoring at least a mention of in-network providers and perhaps closer adherence to the ACA language.

Dr. Moore (AIM) expressed a preference for the original language. Even though it is more detailed, it is more accurate. When reading it, there is so much confusion regarding what is and is not covered, the particular component about in-network providers for private insurers is a major issue operationally for immunization programs educating the public about where to obtain vaccines.

Ms. Pellegrini strongly agreed with Dr. Moore and expressed a preference for the original language with its greater level of detail and accuracy. She asked whether it would be appropriate to offer a motion at this state. Dr. Temte replied that it would. Ms. Pellegrini offered a motion to revert to the original language. Dr. Temte did not believe this rose to the need for a full motion and vote, but asked whether it would be acceptable to the WG to revert to the original language. This was acceptable to everyone.

Regarding revaccination post-HCT, Dr. Bocchini pointed out that 24 months after stem cell transplant, YF vaccine could be administered.

Dr. Strikas responded that if this is in the current recommendations, it can be addressed in the General Recommendations.

Dr. Temte asked whether there was general agreement to make this addition without a motion and vote. This was acceptable to everyone.

Dr. Bennett asked whether there were any data regarding how many states have adult IISs, and whether it is required.

Dr. Kempe responded that they do not specifically have adult IISs, but the majority of states do have the ability to enter adult records. She did not know how many actually do enter adult records.

Dr. Moore (AIM) added that CDC publishes data annually on the status of IISs. Her recollection was that over 40 states have lifelong registries in which adult records can be included. The point is well-taken that many adult providers do not realize this, but with Meaningful Use and forcing providers to send EHR information to IISs, the word is getting out that providers of immunizations can send their information to IISs in most states. The IISs need to be used much more effectively, and providers need to be aware of their capacity. The programs are committed to educating adult providers about the benefits.

Dr. Hahn (CSTE) added that in many states, IIS use is only required for children but is available for use in adults. With the move for promoting IISs for adults, the data should become more robust over time.

Dr. Temte commented that Wisconsin has a very functional registry that has a huge amount of population data for adults. He uses this on a daily basis and it is tied directly into their Epic EHR so that they do not have to go outside of the firewall to bring the data in. His mission has been to encourage people not to trust the data within Epic, but to always go to the IIS because the reliability is so good. There is a difference between a state registry being able to and actually doing so, so this is where a lot of emphasis should be placed on this.

Ms. Hayes (ACNM) indicated that the ACNM has been trying to promote the IIS among midwives who are vaccinating their patients. They have found that the CDC website is outdated, though it is not really CDC's fault. She was not sure that if they promoted the CDC site for IIS, it would offer the most current data. In many states, the public health departments have been so gutted financially, they do not communicate the current status. She suggested that if something was included in the General Recommendations, that it would guide clinicians to their own states rather than CDC's list.

As a practicing physician, Dr. Fryhofer (AMA/ACP) shared something that occurred approximately a year ago. She was trying to determine the pneumococcal vaccination history for a patient. She wrote a prescription for Prevnar®, which the patient took to the pharmacy. It was not in the immunization registry. Nothing was ever faxed to her. She called the pharmacy, CVS, which did give the vaccine but said they are not the ones who put it in the immunization registry. It goes to a corporate office which does it. It took an hour to determine whether this patient had her pneumococcal vaccination. Perhaps the General Recommendations could contain a statement that pharmacists need to do this as well.

Dr. Foster (APhA) suggested adding the APhA website to the list of immunization resources. Pharmacies are governed by pharmacy practice laws in each individual state; therefore, every state will be different in terms of what is required for the registry. If it is required in Georgia for example, that would be regulated by the State Board of Pharmacy. Corporate complications also occur. It is not possible to make a broad statement about how this is handled throughout the country.

Dr. Kempe emphasized that her original point was that many providers do not even know about the existence of an IIS or what it is. At a minimum, she thought they should indicate that each state or region has an IIS and that each provider needs to be in touch with their state IIS. Information about how to do that should also be included. In Colorado, there is pretty sophisticated use of the adult side as well. CVS, Target, and other providers are submitting data to the system. But, this is highly variable.

Dr. Temte asked whether any language needed to be added or changed with regard to this issue.

Dr. Belongia suggested that a possible addition would be to state that, “Providers should be aware of state and/or regional IISs and requirements for reporting.”

Dr. Strikas concurred with the suggested language and indicated that the most recent data could be cited about the number of states that have the capability to include adult data, and that providers should be aware of this. There is some language in the Adult Standards that could perhaps be included as well.

Dr. Temte asked if this would be acceptable to everyone. This was acceptable to everyone.

Dr. Bennett emphasized that there is a major difference between “availability” and “requirement.” She was curious regarding the CDC’s progress in working with health departments to make adult vaccine reporting a requirement.

Dr. Schuchat indicated that strengthening the IISs has been a major priority, and CDC has been putting substantially more resources into this effort. An Intergovernmental Advisory Committee has been established to advise about CDC’s strategic plan and priorities. The resources allocated to states and other third party groups for IIS have been increased. A lot of innovative work is underway, such as with the pharmacy-registry interfaces. The requirements are state-driven, so CDC does not do this. However, the agency believes that making use easier is the best plan. Bidirectional flow is the direction of the field, and CDC has been extremely supportive in terms of large financial investments.

Dr. Fryhofer (AMA/ACP) stressed that this is not about state requirements. This is about taking care of patients. This should be a very patient-centered statement that the right thing to do,

when so many different people are administering immunizations, is to enter the information into the IIS. If that is too hard, it should be given to a provider. Keeping the information in a little pharmacy and not sharing it with the world does not help patients or the bottom line. These are expensive vaccines and patients need them.

Dr. Moore (AIM) expressed appreciation on behalf of the states for the additional funding being received to make the IISs more robust, and they are working very hard on this. She agreed that the focus should not be on requirements for use. For example, requirements are prohibited in Tennessee. Given the way the law was founded, providers cannot be required to report. Instead, the system is made as useful, useable, and valuable to the clinician in the provision of patient care so that they couldn't imagine not using it. The problem is that they do not necessarily know about it and all of its wonderful benefits yet, but AIM is working on that and is adding an increasing number of clinicians each day whose data are being submitted from their EHRs. That does include pharmacies, and AIM is very grateful to the pharmacies that are submitting their information into the IIS. The immunization neighborhood works best when everyone knows what everyone else is doing. The IIS is the heart of that neighborhood where everyone has the ability to open the door and see what the patients have received. Any support for getting people engaged will be greatly appreciated regardless of the patient's age. They recognize that adult providers really need to be brought on board, because with the expanding adult schedule, there is so much benefit for patient care in knowing what others have done.

Dr. Dwelle (ASTHO) indicated that North Dakota has some challenges in the interoperability and bidirectional flow of immunizations between the Native American populations and the immunization registry. This is one area in which federal partners could encourage bidirectional flow.

Vote: Second Half of General Recommendations

Dr. Bocchini made a motion to approve the second half of the General Recommendations as presented, with the suggested language changes regarding ACA, YF after HCT, and IIS. Dr. Vázquez seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vázquez
0 Opposed: N/A
0 Abstained: N/A

Novel Influenza Vaccines

Introduction

Doug Campos-Outcalt, MD, MPA
Novel Influenza Vaccines Work Group
Advisory Committee on Immunization Practices

Dr. Campos-Outcalt reminded everyone that the ACIP Novel Influenza Vaccines WG was formed in February 2014, at which time the WG was charged with developing recommendations for use of influenza A (H5N1) vaccine during interpandemic periods. October 2014 ACIP meeting presentations included an update on influenza A (H5N1) epidemiology and vaccines, and GRADE and policy options for influenza A (H5N1) vaccine. A vote was planned for the February 2015 ACIP meeting; however, the Novel Influenza Vaccines session was cancelled due to impending inclement weather and was moved to the June 2015 meeting.

Although a vote was intended during this session, in addition to the 2014 production delays following the Quebec plant inspection[1], additional delays were predicted for 2015-2016 due to manufacturing upgrades at that plant [[1]http://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm401719.htm]. The current schedule is to produce a Q-Pan H5N1 lot in mid-2017]. Given the changing manufacturer's schedule, an influenza A (H5) epidemiology update was presented and no recommended policy vote was entertained during this session. The WG will go into semi-hibernation and will be reconstituted closer to the time when the vaccine will be available. Any changes will be incorporated and recommendations for a vote will be brought forward at that time.

Influenza A (H5) Epidemiology Update

Sonja J. Olsen, PhD
National Center for Immunization and Respiratory Diseases
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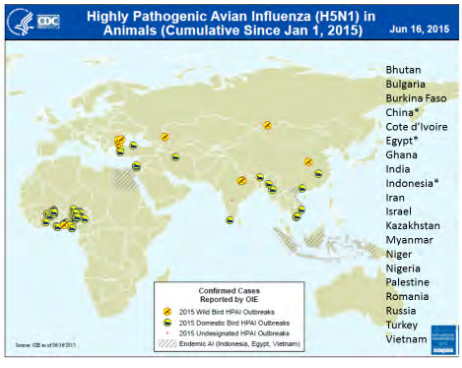
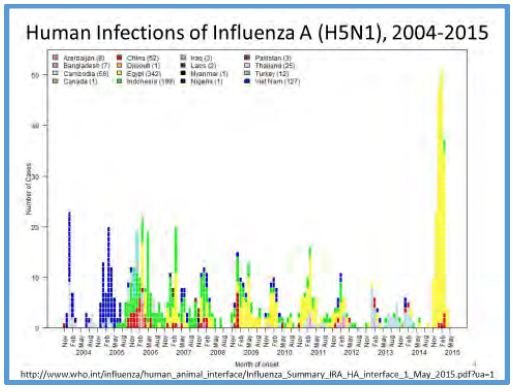
Dr. Olsen provided an update on global epidemiology of H5N1 in humans and birds, an update on H5 found in US birds, and data on Q-Pan H5N1 cross-reactivity to some of these viruses. Since 2003, the Eurasian origin H5N1 viruses have spread in animals to 65 countries. As shown on the following map, H5N1 viruses have been found in birds in 20 countries in 2015:



In three of the countries shown on the map (China, Egypt, and Indonesia), the virus has also been confirmed in humans in 2015.

In the following graphic, the number of human H5N1 virus infections are shown by country between 2003 and 2015. Infections from each country are shown in a different color:



Between November 2003 and May 1, 2015, there have been 840 cases in humans reported to the World Health Organization (WHO) from 16 countries. These cases have resulted in 413 deaths, which is a mortality of 53%. In yellow at the right side are the recent cases, showing a large upsurge in H5N1 cases in humans in Egypt. This upsurge is the highest number of cases reported by a country in a similar time period. In 2015, there have been 132 cases in humans in Egypt.

H5N1 viruses are now circulating in all sectors of poultry production throughout Egypt. This likely reflects changes in the economy and poultry industry. Many small farmers are raising poultry in a largely unmonitored and uncontrolled farming sector. The hemagglutinin (HA) gene continues to evolve; however, experts do not think the recent upsurge in human cases is due to changes in the virus. Instead, the increase in human infections is likely because of an increase in persons exposed to infected poultry. In the last month, cases have been decreasing. There have been fewer outbreaks in poultry, increased public health awareness, and probably some seasonal risk factors that are not fully understood.

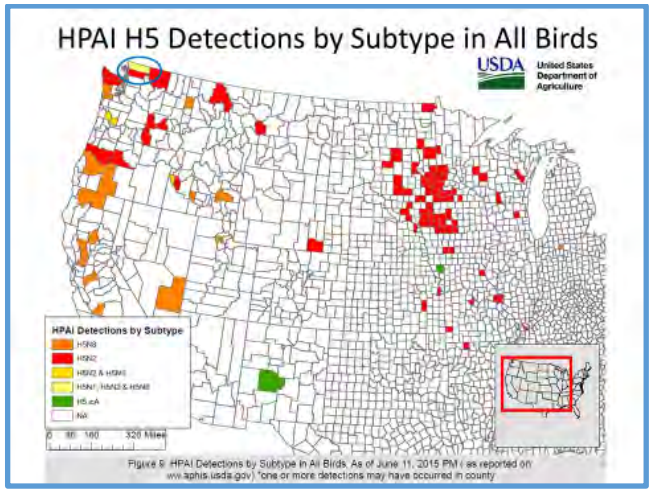
Another recent event is the detection of highly pathogenic avian influenza (HPAI) viruses in the US. In response to detection of HPAI H5N2 virus among commercial flocks in Canada in early December 2014, the US increased surveillance in wild birds along the US/Canada border and in the Pacific Flyway. Three novel viruses have now been found in wild birds and poultry in the US in commercial poultry and wild flocks: a new H5N1 reassortant[1], H5N8, H5N2[2]. The H5N1 virus is different from the Eurasian H5N1 virus. These three viruses in the US are highly pathogenic in chickens. They are reassortants viruses with an HA from a Eurasian H5N8 virus and are designated as a new Clade (2.3.4.4). The N2 and N8 are from a North American avian influenza. The neuraminidase is different from the strains causing illness and death discussed earlier [[1]Different from Eurasian H5N1 virus causing human illness and death; [2]N2 and N8 are different from strains circulating in Asia, Europe and Africa].

The following table shows the number of HPAI H5 Detections in the US between December 14, 2014 and June 9, 2015:

Species	H5N2	H5N8	H5N1	H5
Poultry	218	4		
Captive Wild Bird	3	2		
Wild Bird (as of 5/14)	35	22	3	12
Total # detections	256	28	3	12

The United States Department of Agriculture (USDA) and states have mounted a very large response, responding quickly with quarantine, eradication with indemnity, monitoring, disinfecting, and testing to confirm virus-free premises. To date, over 47 million birds have been affected.

The following map shows the geographic distribution of HPAI detections by H5 subtype:



The blue circle in the Pacific Northwest is the location of the three H5N1 viruses detected in wild birds. The majority of detections are concentrated as a whole in two migratory pathways, the Pacific and the Mississippi Flyways. USDA scientists believe that wild birds introduced the viruses into commercial poultry. Although no humans have been infected to date, CDC is working with USDA and local and state health departments to monitor for illness in persons exposed to infected birds or contaminated surfaces.

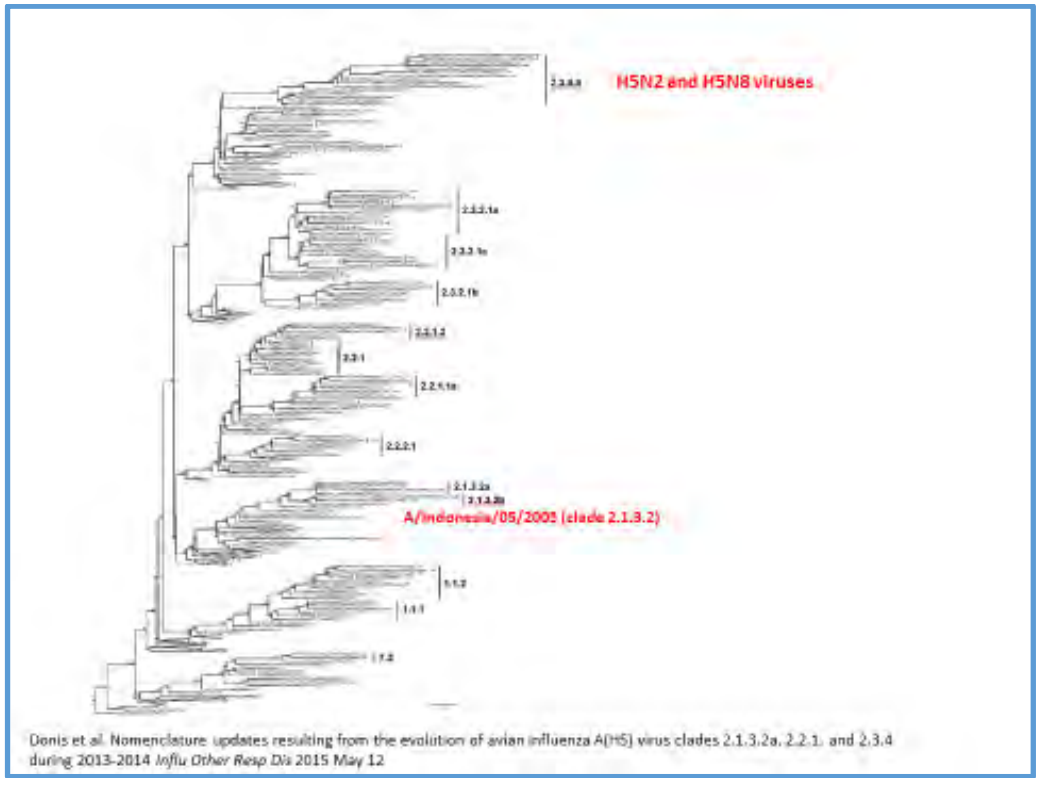
In terms of the number of HPAI avian influenza-infected premises detected between December 10, 2014 and June 11, 2015, the majority of outbreaks (~90%) were detected in commercial poultry and chicken egg layers. Outbreaks may have peaked, as the number of detections has decreased in recent weeks.

Given the changes in the epidemiology of H5N1 virus clades circulating globally and the detection of new H5 viruses in birds and poultry in the US, CDC wanted to determine whether the Q-Pan H5N1 vaccine cross-reacted with any of these viruses. There are no published data, but CDC was able to test a small number of sera from two vaccine studies—one from GSK and one from CDC. The sera were tested against viruses by microneutralization assay as this

assay is considered to be more sensitive than the HA inhibition assay. While these data are not currently published, they will be submitted for publication in the near future.

CDC looked at the percent ≥4-fold increase in microneutralization antibody titers in Q-Pan H5N1 vaccine sera when challenged against other H5N1 viruses recently circulating in humans. Overall there was some cross-reactivity to the viruses. However, the response varied by clade. The response was fairly strong for the 2010 Egypt virus. Then CDC looked at the microneutralization antibody titers in Q-Pan H5N1 vaccine sera when challenged against the two new H5 viruses circulating in poultry in the US. The response was robust against the homologous vaccine strain, A/Indonesia/05/2005 (H5N1), was robust. In contrast, there was essentially no response to the two poultry viruses (H5N8 and H5N2). The data using vaccine sera from both the GSK and CDC studies showed similar results.

H5 viruses are grouped into clades based on their phylogenetic characterization and sequence homology of the HA gene. The HA gene of H5N1 viruses evolves in nature. It has evolved into many genetically and antigenetically distinguishable clades. The H5 viruses in birds in the US are part of a newly designated clade 2.3.4.4. The following phylogenetic tree shows the evolutionary distance between those viruses and other viruses, including the Q-Pan H5N1 vaccine shown toward the bottom of the graph:



Donis et al. Nomenclature updates resulting from the evolution of avian influenza A(H5) virus clades 2.1.3.2a, 2.2.1, and 2.3.4 during 2013-2014 *Influ Other Respir Dis* 2015 May 12

In other words, they are evolutionarily distant, and thus perhaps it is not surprising that there was no cross-reactivity.

Overall, it was found that the H5N1 Q-Pan vaccine offered some level of cross-neutralizing antibody titers to H5N1 viruses from various clades, including newly emerging strains. Cross-clade responses vary between clades and viruses. The responses varied by clade and were generally lower that the response to the homologous vaccine strain. However, the response was robust to the clade 2.2.1 Egypt virus. In contrast, the vaccine (clade 2.1.3.2) elicited no neutralizing antibodies to the new H5N2 and H5N8 (clade 2.3.4.4) viruses found in poultry in the US. Additionally, where possible, evaluating cell-mediated cross-reactive immunity may be helpful to better understand the potential for vaccines to provide some level of cross-protection.

In summary, HPAI H5N1 viruses continue to circulate globally and cause illness and death in humans. The most recent upsurge in Egypt was the result of increased poultry infections combined with increased interactions between infected birds and humans. The H5 viruses (H5N2, H5N8) in US birds are different from the Eurasian H5N1 viruses and thus far have not caused any illness in humans. Q-Pan H5N1 vaccine is cross-reactive with recently circulating Eurasian H5N1 viruses, but not with H5N2 or H5N8 in US birds. CDC is developing a candidate vaccine virus specific to the H5 viruses in the US that could be used to make a vaccine if one were needed. CDC and WHO will continue to monitor the global situation of avian influenza.

Discussion Points

It seemed surprising to Dr. Belongia that there have been so many flocks affected in the US over the past several months, but there have not been any instances of known transmissions to humans. He asked whether there were any ideas regarding why that might be the case.

Dr. Olsen responded that CDC has been conducting some monitoring. Approximately 30 of 1100 people, largely farm workers, have been exposed and gotten a respiratory illness. All of them have tested negative to date. It may be that the virus is not well-adapted, but the answer to why there has been no transmission to humans is not really known.

Dr. Temte wondered whether the HAs in the three H5 viruses circulating in birds in North America were identical or similar. Regarding the graph showing the indication that the current avian epidemic in the US appears to be waning, he wondered whether there was an expectation that this would be on the upswing by October and whether anything is going to be done in terms of assuring poultry workers are vaccinated with appropriate seasonal influenza vaccine to reduce the risk of potential co-infection. In his state, a number of poultry workers tend to be people who may be undocumented and may be high risk individuals in terms of lack of usual medical assessments. It would be beneficial to be proactive.

Dr. Olsen replied that the HA is similar, though she was not certain whether it was identical. In terms of the apparent waning of the current avian epidemic, the current thinking is that it may be decreasing in birds and poultry in the US. But, the expectation by USDA is that it will likely increase again in the fall because a seasonal pattern to these viruses has been observed globally for the Eurasian H5N1. There are recommendations for response workers to be vaccinated. Response workers include the 1100 farm workers, as well as approximately 2000 to 4000 USDA direct hires and contractors who are response workers. There are written recommendations from the USDA for their response workers, including poultry cullers. She thought the former category (farm workers) was probably what Dr. Temte was referring to. There are US recommendations to vaccinate everyone 6 months of age and older. Although she did not know what specific states were doing in terms of outreach, CDC can find out.

Dr. Dwelle (ASTHO) found it interesting that none of these poultry infections were being observed in the wintering grounds of wild birds. They are migrating North at this point, and he wondered whether there was any indication of why this was occurring in those reaching their summer nesting grounds.

Dr. Olsen replied that the viruses have different prevalences in different species and can affect them differently. Some viruses cause overt clinical illness and some do not. Ongoing surveillance and/or testing only birds that die may be factors.

Dr. Sun (FDA) noted that in assessing cross-neutralization with the H5N1 sera in humans against the avian H5 strain, nothing was found. He asked whether HA inhibition assay was utilized to determine whether there was cross-neutralization.

Dr. Olsen responded that CDC did not use that assay. They used only the microneutralization assay because it is accepted to be a more sensitive assay. They thought they would be more likely to find something with the microneutralization assay than the HA inhibition assay, so they did not test using the HA inhibition assay.

Dr. Temte reminded everyone that this WG would remain dormant until vaccine becomes available. The decision was that they did not want to have an approved recommendation with no ability to provide vaccine.

Influenza Vaccines

Introduction

Ruth Karron, MD
Chair, Influenza Work Group

Dr. Karron reported that since June 2014, the Influenza WG has focused primarily on 2013-2014 vaccine effectiveness estimates for live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV). They have heard data from the US Flu VE Network, the Armed Forces Health Surveillance Center, and MedImmune on a post-marketing study of quadrivalent LAIV. She indicated that during this session, updates would be presented on influenza vaccine effectiveness, quadrivalent intradermal influenza vaccine, influenza vaccine safety, and high-dose influenza vaccine.

Influenza Vaccine Effectiveness Update

Brendan Flannery, PhD
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Flannery presented preliminary end-of-season estimates of influenza vaccine effectiveness for the 2014-2015 season from the US Flu Vaccine Effectiveness Network. Data were provided by US Flu VE Network sites and were analyzed at CDC by Jessie Clippard, Data Manager.

Based on influenza surveillance data from US public health sites comparing the 2014-2015 season with the two previous seasons, influenza A(H3N2) virus predominated during 2014-2015 as it did in 2012-2013, with circulation of influenza B virus during the second half of the season after January. Influenza A(H1N1)pdm09, which predominated during 2013-2014 season, circulated at very low levels in 2014-2015. Thus, there were no additional data to provide on VE for the H1N1 virus.

The five institutions and Principal Investigators (PIs) participating in the US Flu VE network are as follows:

- Group Health Cooperative: PIs Lisa Jackson and Mike Jackson
- Baylor Scott and White Health: PI Manju Gaglani
- Marshfield Clinic Research Foundation: PIs Ed Belongia and Huong McLean
- University of Michigan: PIs Arnold Monto and Suzanne Ohmit
- University of Pittsburgh: PIs Rick Zimmerman and Patricia Nowalk

As a reminder, methods for the Flu VE Network have been presented previously. This analysis includes outpatients enrolled from November 10, 2014 through April 10, 2015, when influenza cases were identified at the five VE network sites. VE is estimated from the odds ratios comparing vaccination among influenza virus-positive case patients to influenza virus-negative patients as the comparison group. Influenza virus was tested using polymerase chain reaction (PCR). Vaccination status was determined as for interim estimates. Partially vaccinated children are excluded from this analysis.

This season for the first time, it was possible to estimate VE for specific groups of H3N2 viruses classified by HA gene relatedness. Hemagglutination inhibition (HI) assays are normally used to characterize circulating influenza viruses as “vaccine-like” or “low reactors” to vaccine as a measure of antigenic difference or drift. Most, or more than 80%, of the H3N2 viruses tested at CDC by HI were low reactors or antigenically drifted from the 2014-2015 vaccine component A/Texas/50/2012. In addition, many H3N2 viruses could not be characterized by HI due to changes in the properties of the virus. As a result, CDC used genetic sequencing to characterize H3N2 viruses and inferred antigenic properties based on viruses that could be characterized by HI. Several genetic groups of H3N2 viruses co-circulated during the season, providing the opportunity to compare VE by genetic group. VE by genetic group is calculated the same way as for all influenza viruses, except that cases are restricted to a specific HA genetic group.

It was a banner year for the Flu VE network. A total of 9707 patients were enrolled at the five VE network sites, including over 3700 children and adolescents and 1200 patients 65 years of age and older. Overall, 24% of those enrolled tested positive for influenza by reverse transcription polymerase chain reaction (RT-PCR) and 76% were RT-PCR-negative. Of the influenza cases, 83% were type A and all subtyped A viruses in the network were H3N2. Among the 17% of enrollees who tested positive for influenza B virus, 85% were the B-Yamagata lineage that is in both the trivalent and the quadrivalent vaccines and 15% were B-Victoria lineage included in quadrivalent vaccines. Overall, 53% of patients were considered vaccinated. Among vaccine types, 51% of all inactivated vaccines were quadrivalent, 49% trivalent. Live-attenuated vaccine accounted for 26% of vaccines among 2 through 17 year olds, and 9% of vaccinated patients 65 years and older received high-dose vaccine.

In terms of numbers of patients enrolled per week by RT-PCR result, peak enrollment for H3N2 cases occurred in December during weeks 50 through 52. Numbers of influenza B cases were

low, with only a slight increase in March. The overall adjusted VE against any influenza virus was 23% and was statistically significant. VE ranged from 10% (non-significant) among 18 through 49 year olds to 36% (significant) among patients 65 years and older. For patients of all ages combined, adjusted VE for any influenza vaccination was 13% against H3N2, 55% against B-Yamagata, and 63% against B-Victoria. VE estimates were similar across age groups with overlapping confidence intervals. For H3N2, VE was low in all age groups and confidence intervals crossed zero for all age groups except young children. VE against influenza B virus was higher with some smaller sample sizes leading to large confidence intervals. The highest point estimate was seen in patients 65 years and older.

Low VE against H3N2 viruses was consistent with predominance of one genetic group, 3C.2a, among H3N2 viruses sequenced from US laboratories or from the US Flu VE network. Most viruses tested from the predominant genetic group were low reactors to vaccine by HI. A smaller percentage of viruses belonged to groups 3C.3 or 3C.3b, which were characterized by HI as vaccine-like. Of note, although only 3% of sequenced viruses belonged to group 3C.3a, which includes the A/Switzerland virus chosen as the H3N2 component of the 2015-2016 vaccine, groups 2a and 3a share antigenic properties. With the sequenced viruses from the US Flu VE network, it was possible to estimate VE against the predominant genetic group of antigenically drifted H3N2 viruses and one vaccine-like genetic group, 3C.3b. Compared to VE against all H3N2 genetic groups combined, VE against the more vaccine-like group 3b viruses was 43% and statistically significant, while VE against the antigenically drifted group 2a viruses was not significant.

Regarding VE against any influenza by vaccine type, adjusted VE for quadrivalent live-attenuated vaccine against any influenza was 9% overall with confidence interval including zero, with similar estimates for younger and older children. Adjusted VE for inactivated vaccine against any influenza was 31% and was statistically significant. Adjusted VE against H3N2 among 2 through 17 year olds was slightly lower at -8% (-44% to 19%) for LAIV and 17% (-4 to 33%) for inactivated vaccines. Results were similar when the comparison was limited to quadrivalent inactivated vaccines and medical record documented doses:

- Quadrivalent inactivated, IIV4, 892 (45%)
- Trivalent inactivated, IIV3, 560 (28%)
- Quadrivalent live-attenuated, LAIV4, 509 (26%)

In terms of the comparison by influenza type and B lineage, adjusted VE estimates against H3N2, B, or B/Yamagata lineage were similar for IIV and LAIV. VE was low for H3N2 for both vaccine types, and neither was statistically significant. VE against influenza B and B/Yamagata was higher for both IIV and LAIV.

VE was also compared for high-dose and standard-dose inactivated vaccines compared to unvaccinated among patients 65 years of age and older. However, these estimates were not adjusted for comorbid, high-risk conditions. VE for high-dose vaccine against any influenza was 14% and was not statistically significant. VE for any standard-dose inactivated vaccine was 31% and for trivalent standard dose vaccine was 38%, and both were statistically significant. VE against H3N2 was lower for both vaccine types and was not significant, and relative effectiveness of high-dose to standard dose showed no significant difference between the two vaccine types. These are preliminary data.

There are several important limitations. Some estimates are imprecise due to small numbers of patients in specific groups (e.g., VE for high-dose, VE for live-attenuated by age group, and VE for less common H3 genetic groups). As customary with an observational study design, there is a potential for confounding due to differences in patient characteristics among vaccinated/ unvaccinated or by vaccine type.

In conclusion, reduced VE is consistent with predominance of antigenically drifted A(H3N2) viruses. H3N2 accounted for 83% of influenza-positive cases at US Flu VE Network sites. The majority (>80%) in the predominant HA genetic group 3C.2a were characterized as low reactors to vaccine. There was higher VE against less prevalent vaccine-like A(H3N2) viruses and influenza B viruses. VE was 66% to 67% against influenza B for LAIV and IIV, respectively, among children and adolescents. There was reduced or non-significant VE against A(H3N2) for any vaccine type, including LAIV and IIV in children, as well as high-dose and standard-dose among persons ≥65 years of age.

Discussion Points

Dr. Karron recalled the low VE of approximately 43% for 156 cases against H3N2 for vaccine-like strains belonging to HA group 3C.3b. She wondered whether LAIV could be split out for the viruses that were like the ones in the vaccine.

Dr. Flannery replied that the estimate against the genetic groups that were vaccine-like for LAIV and IIV were both higher, which is similar to what he showed for all age groups. Neither estimate is significant compared to the unvaccinated group. It is just that the sample sizes are small. This is consistent with the same trend observed for any vaccine for which LAIV and IIV seem to have better effectiveness against the vaccine-like virus than against the drifted viruses belonging to HA group 3C.2a.

Regarding vaccine effectiveness by age group, Dr. Sun (FDA) thought it seemed like 18 through 49 years olds have the lowest VE. He wondered whether that was because most strains are unmatched and if that explained the low efficacy in the middle age group.

Dr. Flannery said he did not have an explanation for this, and that it was not as simple as a difference in distribution by genetic group. The pattern looks very similar for just H3N2s, but it was not broken down by vaccine-like and non-vaccine-like groups. Even the early estimates were lower for the 18 through 49 year old group, but the reason is unknown.

Dr. Gemmill (NACI) wondered whether it could be surmised that the reduced VE for LAIV that was presented in October was well behind them, and if Dr. Flannery could make any comments about that.

Dr. Flannery responded that the only reduced effectiveness observed during the 2013-14 season was against the H1N1 pandemic strain. There was not enough pandemic H1N1 virus circulation in 2014-15 to have an estimate for LAIV against H1N1. MedImunne presented data which suggested that LAIV effectiveness in 2013-14 was good against B. These data are consistent with good effectiveness against B in 2014-15, but are not helpful at all with more information about H1N1. VE against H3N2 was not very good for either vaccine this year with this much antigenic drift.

Dr. Decker (Sanofi Pasteur) observed that they were asking an interesting set of questions from the data, but were not getting robust answers back because of the sample size limitations. He

asked whether there was hope that in the future the surveillance population would be expanded.

Dr. Flannery replied that the question for ACIP in the past has regarded how well the vaccine is working overall. There is increasing interest in breaking out vaccine type, and for the first time there are data comparing high-dose versus standard-dose. The analyses are also dependent upon uptake of the various vaccines. In the last several years, there have been estimates for LAIV and this is the first year that an estimate could be presented for high-dose. As new vaccines are introduced, it is going to be very difficult to increase sample sizes and keep up with the vaccines. There are no plans to expand the network with the objective of trying to estimate vaccine type-specific VE estimates, but the numbers enrolled are being increased to assess the types of estimates presented in the past against what circulates by age group and some of the predominant vaccine types.

Dr. Schuchat added that it is extraordinary how much data there are by age, vaccine type, and serotype in June. There were also a lot of data in January. Ten years ago, these types of data would be provided overall two or three years after the season. It is extremely helpful to have this large a sample size now for children and the elderly, and it is very useful for ACIP to be able to reflect on it. It does not mean that the answers are going to be clear with clean, tight confidence intervals. But with a moderate to low efficacy product, even with a very large sample size, the confidence intervals might not be clear.

Dr. Belongia pointed out that it was an understatement to call this "surveillance." This is a highly resource-intensive activity that requires many people and resources yearly. It is clearly paying off in terms of data and utility.

Dr. Sawyer (PIDS) commented that pediatricians and young children of the world are hanging on ACIP's every word about LAIV effectiveness. There was a preferential statement. Now there is not a preferential statement. The point estimates make him wonder whether it is now inferior for some reason. He sees that the confidence intervals are very wide, but he would hope that there might be some opportunity to tighten those confidence intervals for that age group in order to resolve the uncertainty pediatricians are facing this year in trying to determine which vaccine to use.

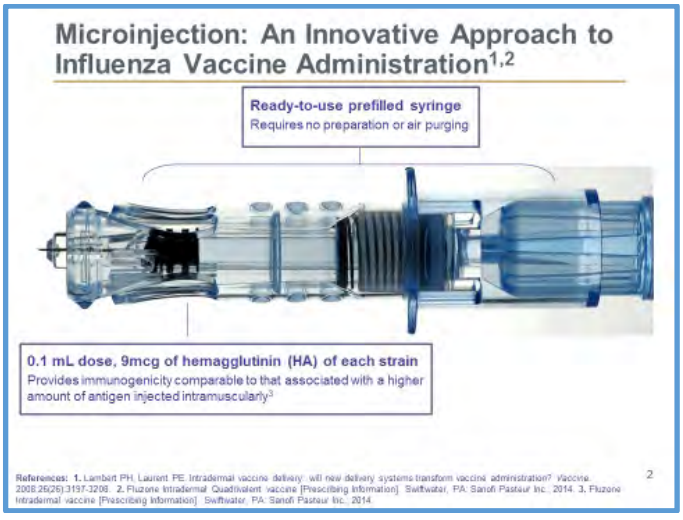
To underscore Dr. Schuchat's comments, Dr. Baker (IDSA) noted that most hospitals are not currently performing viral cultures. This kind of work cannot be done without isolates. They are using PCR and indicate A or B at most. She agreed that the amount of data available is incredible. It is imperative in the molecular era, in virology, to have viable virus isolates, especially with influenza.

Wayne Hachey (Protein Sciences Corporation) reported that Protein Sciences Corporation conducted a clinical trial during this season in adults over 50 years of age. Those results became available about 24 hours before this meeting. Preliminarily, in the over 50 group, the attack rate was 50% less than the comparator. Whether it is having three times the amount of antigen or not having to deal with an egg-grown vaccine virus is unknown, but it does appear that the vaccine was reasonably effective during this past influenza season. For the subgroup 75 years of age and older, the attack rate with the comparator was 40% and with Flublok® was 25%. They will share additional data with the WG as it becomes available.

Quadrivalent Intradermal Influenza Vaccine

Corey Robertson, MD, MPH
Sanofi Pasteur

During this session, Dr. Robertson presented an update on Fluzone Intradermal® quadrivalent vaccine (QIV-ID). In 2010, Sanofi Pasteur first introduced the intradermal influenza vaccine to the US in a trivalent formulation. The quadrivalent formulation was licensed in December 2014. For the 2015-2016 season and beyond, Fluzone Intradermal® will be available only in a quadrivalent formulation. Doses will be available for the upcoming season. For those unfamiliar with the Fluzone® intradermal vaccine, Dr. Robertson shared the following image of the microinjection system used for Fluzone Intradermal® quadrivalent:



The microinjection system consists of a ready-to-use, prefilled syringe that does not require air purging and contains a 0.1 mL dose of vaccine. Probably the most salient feature of the microinjection system is the feature that is barely visible—the microneedle that is pre-attached to the syringe. This microneedle is 30-gauge in diameter and about 1.5 millimeters in length, which is about the width of a penny. The length of this microneedle ensures that the vaccine is deposited within the dermal layer of the skin of young adults regardless of their gender, race, or body mass index (BMI). Another component of the microinjection system is the integrated needle shield that can be activated after vaccination. This needle shield covers the microneedle and may help reduce the risk of injury to healthcare personnel.

Years ago, Sanofi Pasteur conducted studies to show that the trivalent formulation of Fluzone Intradermal® vaccine induced immune responses that were comparable to the Fluzone® vaccine that is injected intramuscularly. Building upon that experience, Sanofi Pasteur embarked upon a clinical development program that consisted of a Phase 3 clinical trial, which is referred to as QID01. This was a randomized, double-blind, active-controlled trial that was conducted in multiple centers across the US during the 2012-2013 influenza season. More than 3300 adults 18 through 64 years of age participated in the trial, and they were randomly assigned to receive one of the three study vaccines: QIV-ID or either one of two trivalent intradermal controls. All of the study vaccines contained the same A strains, but they differed with respect to their B strain compositions as shown in the following table:

IIV4-ID N=1676	IIV3-ID(1) N=837	IIV3-ID(2) N=847
A/Brisbane/59/2007(H1N1) A/Uruguay/716/2007(H3N2) B/Texas/6/2011 (Yamagata) B/Brisbane/60/2008 (Victoria)	A/Brisbane/59/2007(H1N1) A/Uruguay/716/2007(H3N2) B/Texas/6/2011 (Yamagata)	A/Brisbane/59/2007(H1N1) A/Uruguay/716/2007(H3N2) B/Brisbane/60/2008 (Victoria)

Each vaccine was formulated to contain 9 micrograms of hemagglutinin per strain per 0.1 mL dose, and each subject received his or her assigned vaccine on Day 0 of the study.

Data were collected for safety and immunogenicity as is typically done in Sanofi Pasteur's influenza vaccine clinical trials. Monitoring was done for immediate reactions within 30 minutes after vaccination, solicited reactions within 7 days after vaccination, unsolicited AEs within 28 days after vaccination, and SAEs within 6 months after vaccination. HAI responses were assessed by collecting specimens before and approximately 28 days after vaccination. About two-thirds of the trial population was randomly selected to participate in the immunogenicity assessment. The endpoints were post-vaccination GMTs, seroconversion rates, and seroprotection rates.

Regarding the study results, injection-site pain was the most commonly reported injection site reaction among all vaccine groups. Vaccine rates of pain, pruritus, and erythema at the injection site were comparable across the three vaccine groups. Reactions were primarily Grade 1 or 2 in intensity and were self-limiting. A similar pattern was observed for injection site reactions of swelling, induration, and ecchymosis, albeit at frequencies that were far lower than for pain, pruritus, and erythema at the injection site.

In terms of solicited systemic reactions, approximately one-third of the participants in each vaccine group experienced myalgia, headache, or malaise. Fever was a rare occurrence in the study, with less than 1% of participants in each vaccine arm experiencing that outcome. Rates of unsolicited AEs and SAEs were comparable across the three vaccine groups. One death was reported in this study, which occurred in a 60 year old man who had risk factors for coronary disease. He had a fatal myocardial infarction on Day 177 of the 180-day safety follow-up period. At rates of about 20%, comparable proportions of quadrivalent and trivalent recipients experienced either a Grade 2 or Grade 3 solicited systemic reaction. Likewise, comparable proportions of QIV and trivalent recipients experienced a Grade 3 solicited injection site reaction, at 4% and 3.1%, respectively.

With respect to immunogenicity, post-vaccination GMTs+ 28 days after vaccination for the quadrivalent formulation were comparable to those observed for the trivalent controls for all four vaccine strains. For the B strain responses following use of the trivalent controls that did not contain both B strains, the GMT responses were about half of those observed for the quadrivalent formulation. Based on predefined criteria, QIV-ID induced immune responses that were non-inferior to the trivalent controls with respect to all four vaccine strains and B strain responses were superior to the trivalent controls that did not contain those corresponding B strains.

The quadrivalent formulation induced seroconversion rates that were comparable to those seen following use of the trivalent controls for corresponding strains. Similar to what was observed with the GMT responses, seroconversion rates following use of the trivalent controls for the B strains that were not contained in the trivalent controls were about half of those seen for the quadrivalent formulation. The quadrivalent formulation met all nine inferiority and superiority endpoints.

In conclusion, Fluzone® Intradermal quadrivalent vaccine was as immunogenic and as safe as trivalent intradermal vaccine in a healthy adult population. With inclusion of the second B strain, Fluzone® Intradermal quadrivalent vaccine reduced the risk of B strain mismatch and could help provide improved protection against influenza.

Discussion Points

Dr. Zahn (NACCHO) asked whether other parts of the immune response are similar or fundamentally different for IIV versus intradermal.

Dr. Robertson replied the cell-mediated immunity has been a challenge to assess, and unfortunately there is not currently an answer to whether use of the intradermal vaccine might have another mechanism of action in terms of inducing an immune response.

Ms. Hayes (ACNM/ANA) said it was her understanding that this is the only FDA Category A influenza vaccine, and that there have been clinical trials among pregnant women proving safety.

Dr. Robertson responded that this is a Category B vaccine.

Dr. Sun (FDA) added that the pregnancy categories will be eliminated and there will be a new way to approach labels with regard to pregnancy.

Dr. Reingold asked why it took two years to provide the results from the trial conducted during the 2012-2013 influenza season.

Dr. Robertson replied that it was because it took that long to conduct the clinical trials and license the product.

Influenza Safety Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro presented an end-of-season update on 2014-2015 influenza vaccine safety monitoring based on the Vaccine Adverse Event Reporting System (VAERS) surveillance, the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA), and a recent VSD study that assessed trivalent inactivated influenza vaccine and spontaneous abortion.

As a reminded, VAERS is a spontaneous reporting system, which is co-administered by CDC and FDA. The strengths and limitations of VAERS are those inherent to passive reporting systems in general, including the following:

Strengths	Limitations
❑ Rapid signal detection ❑ Can detect rare adverse events ❑ Generates hypothesis ❑ Encourages reports from healthcare providers and accepts reports from patients and others ❑ Data available to the public	❑ Reporting bias (e.g., underreporting, stimulated reporting) ❑ Inconsistent data quality and completeness ❑ Not designed to assess if vaccine caused an adverse event (AE) ❑ Lack of unvaccinated comparison group

For VAERS surveillance, US influenza vaccine reports received through May 22, 2015 were assessed for individuals who were vaccinated from July 1, 2014 through May 1, 2015. Signs, symptoms, and diagnoses were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms. VAERS reports and medical record reviews were conducted for all serious reports following IIV4, LAIV4, ccIIV3, or RIV3; all anaphylaxis reports in persons with a history of egg allergy; and pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, and serious reports. Empirical Bayesian data mining was conducted by colleagues at FDA [Banks et al. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf. 2005;14:601–609].

In terms of US reports to VAERS following IIV3, IIV4, LAIV4 and IIV3-HD, serious reports for all vaccines and vaccine types ranged from about 5% to 6%. Guillain-Barré Syndrome (GBS) reports for all vaccines and vaccine types did not exceed 1%, and anaphylaxis reports were rare. This is similar to data from previous seasons for these vaccines and vaccine types. There were no confirmed anaphylaxis reports with a history of documented egg allergy, and no data mining findings for GBS or anaphylaxis. The numbers were smaller for cell-culture IIV3, recombinant influenza vaccine, and intradermal vaccine. This likely represents lower uptake of these vaccines. Overall, the results were similar to the results for other vaccines and vaccine types. However, the percentages are somewhat more influenced by small numbers. There were no confirmed anaphylaxis reports with a history of documented egg allergy and no data mining findings for GBS and anaphylaxis.

Regarding pregnancy reports in VAERS following influenza vaccination, there were 85 total reports after IIV3 or IIV4. In most of these reports, vaccination occurred during the first or second trimester. In 27% of the reports, a non-pregnancy-specific AE was reported such as an injection site reaction. In 64%, no AE was reported. That total combined is 91% that were not pregnancy-specific. Eight reports had pregnancy-specific outcomes, including six spontaneous abortions, one stillbirth, and one report of vaginal bleeding. There were 18 total reports after LAIV4. As a reminder, LAIV is not recommended during pregnancy. No AEs were reported for 17 of those 18 reports, and there was one report of spontaneous abortion.

In summary, no new safety concerns were detected for IIVs, LAIV4, cell-culture IIV, or recombinant vaccine during the 2014-2015 influenza season. Surveillance for the 2015-2016 influenza season will include enhanced safety monitoring (i.e., clinical review of reports and medical records for selected reports) for Quadrivalent vaccines (IIV4 and LAIV4), ccIIV, and RIV3; pregnancy reports; and reports in persons with history of egg allergy.

Moving on to VSD-RCA for the past season, as a reminder the VSD is a collaboration between CDC and nine integrated healthcare plans that collects data on over 9 million persons per year, or approximately 3% of the US population. The VSD links vaccination data to health outcomes data. Its strengths and limitations are as follows:

Strengths	Limitations
❑ All medical encounters are available ❑ Vaccine registry data ❑ Can calculate rates ❑ Can assess risk of an AE ❑ Can review medical records ❑ Tested algorithm to identify pregnancies ❑ Annual birth cohort = 100k	❑ Sample size may be inadequate for very rare events ❑ Vaccines administered outside of medical home may not be captured ❑ Medically unattended health events not captured ❑ Potential for lack of socioeconomic diversity ❑ Data lags

The RCA outcomes for the past season include anaphylaxis, Bell's palsy, encephalitis, GBS, seizures, and transverse myelitis. Age groups, risk window, and control window are also included for the self-controlled design. As a reminder, there are two RCA designs. The self-controlled RCA design means that a person serves as his or her own control and it assesses cases in the risk window versus cases in the comparison window. The current versus historical design assesses a current group of patients compared to a historical group of comparison patients. The comparison window could be before or after the risk window.

In terms of Dose 1 doses administered for specific vaccines, IIV3 dominates for all ages at 3.4 million doses. There are smaller numbers for IIV4 (251,271), LAIV4 (307,967), and high-dose (103,121). For the subset of doses administered to children 6 through 23 months of age, there were 73,000 IIV3 doses and 86,000 IIV4 doses.

Regarding signal detection and evaluation for two of the outcomes, Bell's palsy and encephalitis, the current versus historical design signaled for Bell's palsy in patients 50-plus years of age following IIV4 in October 2014. This is an automated International Classification of Diseases (ICD)-9 code-based analysis. However, after chart review of cases, it was determined to be a false signal. The current versus historical and self-controlled risk interval designs both signaled for encephalitis following IIV3 in December 2014. No significant clustering was found within the 1- to 21-day risk window. After a chart review of cases, it was determined to be a false signal.

For the outcome of seizures, the self-controlled risk design signaled for seizures in children 6 to 23 months old following IIV3 in December 2014. Dr. Shimabukuro explained that the reason "signals" was shown in quotation marks was because this technically was not a signal. This association has been observed in previous influenza seasons, so it is not a new safety concern. Over 73,000 total IIV3 Dose 1 doses were administered. Five events occurred in the risk window, and one event occurred in the comparison window. The relative risk was 17.5, which was statistically significant. The self-controlled risk interval design had a non-statistically significant elevated relative risk for seizures in children 6 to 23 months old following IIV4. Just over 86,000 Dose 1 doses were administered. There were eight events in the risk window and eight in the comparison. The relative risk of 3.5 was not statistically significant, but approached the critical value of the log likelihood ratio.

To evaluate the increased risk of seizures following IIV3, the data were combined for the 2014-2015 and 2013-2014 influenza seasons. This is the same formulation for the 6- to 23-month old age group. That resulted in a total of 244,000 total IIV3 Dose 1 doses administered to this age group. For IIV3 +/- other vaccines, which could include PCV13, the relative risk was 2.5 and was statistically significant. For children who received IIV3 + PCV13 +/- other vaccines during the same healthcare visit, the relative risk was 5.3, which is statistically significant. For IIV3 +/- other vaccines, but not PCV13, and for IIV3 given alone, the relative risk was not significant.

In summary, signals were detected for Bell's palsy and encephalitis. Both were ruled out for true signals after a chart review of the cases. A statistically significant elevated relative risk was detected for seizures in children 6- to 23-months of age following IIV3, and there was a non-statistically significant elevated risk following IIV4. Further assessment indicated that the risk was highest when IIV3 or IIV4 was administered together with PCV13, and was highest in children 12- to 23-month olds, as has been observed in previous seasons.

A VSD study was led by Dr. Jim Donahue, et al. at the Marshfield Clinic titled, "Evaluating the risk of spontaneous abortion following administration of influenza vaccines containing H1N1pdm09 and H3N2 viral antigens." As a reminder, ACIP has recommended seasonal influenza vaccination for women in all stages of pregnancy since 2004. Available data indicate that IIV is safe during pregnancy. However, limited data exist on IIV safety in the first trimester of pregnancy. Uptake of influenza vaccine in pregnancy increased during the 2009-2010 pandemic influenza season, as well as in subsequent influenza seasons.

Spontaneous abortion (SAB) is a relatively common outcome of pregnancy. SAB is the spontaneous loss of a fetus before the 20th week of pregnancy. Pregnancy losses after the 20th week are referred to as stillbirths. SAB occurs in 15% to 20% of women who know they are pregnant. Most SABs occur during the first seven weeks of pregnancy. The risk factors for SAB include advanced maternal age, smoking, obesity, autoimmune disease, and prior SAB. In a previous case-control study in the VSD in 2005-2006 and in 2006-2007, no association was found with SAB and IIV3[1]. A recent meta-analysis did not find an association between SAB and monovalent H1N1 vaccination[2]. The results of these studies and the meta-analysis were not available when the current VSD IIV3-SAB study was initiated. The largest study in the meta-analysis involved adjuvanted influenza vaccines. Other studies of seasonal IIV3 in pregnancy and SAB have been reassuring[3] [[1]Irving et al. Obstet Gynecol. 2013 Jan;121(1):159-65; [2]Bratton et al. Clin Infect Dis. 2015 Mar 1;60(5):e11-9; [3]McMillan et al. Vaccine. 2015 Apr 27;33(18):2108-17; Chambers et al. Vaccine. 2013 Oct 17;31(44):5026-32; Moro et al. Am J Obstet Gynecol. 2011 Feb;204(2):146.e1-7; Moro et al. Am J Obstet Gynecol. 2011 Nov;205(5):473.e1-9].

Using similar methods to the previous VSD study (2005-2007 data), Donahue et al. conducted a study to assess whether IIV3 containing the influenza A (H1N1) pandemic antigen was associated with SAB during the combined 2010-2011 and 2011-2012 influenza seasons. The primary objective was to estimate the association of SAB with IIV3 in a 28-day risk window. The IIV3 formulation was the same during both seasons and contained the influenza A (H1N1) pandemic antigen. Specifically, the formulation for 2010-2011 and 2011-2012 influenza seasons included the following:

- A/California/7/09 (H1N1)-like virus (pandemic (H1N1) 2009 influenza virus)
- A/Perth/16/2009 (H3N2)-like virus
- B/Brisbane/60/2008-like virus

The primary objective was to estimate the association of SAB with IIV3 in a 28-day risk window. The IIV3 formulation was the same during both seasons. This was a matched case-control design using a 1:1 matching ratio. Cases were women with SAB from 5 to less than 20 weeks gestational age. Controls were women with live births or stillbirths ≥20 weeks gestational age. SAB was identified using ICD-9 codes confirmed through medical record abstraction and adjudicated to confirm SAB and SAB date. The date of SAB was the reference date for each case-control pair. Cases and controls were matched on age (<30, 30+ years), VSD site, and last menstrual period (LMP). Eligibility criteria included the following:

- Women 18 to 44 years old
- Enrolled ≥1 year prior to LMP
- LMP documented in record
- Confirmed intrauterine pregnancy by ultrasound

Vaccine exposure included receipt of IIV3 documented in the medical record. The risk window was 28 days before the reference date, although the investigators also examined risk windows beyond 28 days. Conditional logistic regression was conducted and included the following covariates:

- Maternal age
- Smoking during pregnancy
- History of type 1 or 2 diabetes mellitus
- Concomitant IIV3 and Tdap vaccination
- Pre-pregnancy body mass index
- Previous healthcare utilization

Regarding the preliminary results, there were 485 matched pairs in the final combined analysis. The adjusted odds ratio was 2.0 with a 95% confidence interval of 1.1 to 3.6 for IIV receipt in the 1 to 28 days before SAB compared to unvaccinated women. There was no association in other risk windows. A post-hoc analysis of the 1- to 28-day window was conducted to assess season-specific analyses. For the 2010-2011 season, the adjusted odds ratio was 3.7 with a 95% confidence interval of 1.4 to 9.4. In the 2011-2012 season, the adjusted odds ratio was 1.4 with a 95% confidence interval of 0.6 to 3.3 and was not significant. As a reminder, the vaccine formulation was the same in both seasons.

Also assessed was the association between SAB and IIV3 in a 1- to 28-day risk window restricted to women who received pH1N1-containing vaccine in the previous season. A H1N1pdm09-containing vaccine in the previous season could have been the monovalent or trivalent vaccine depending upon the season. For women who received a H1N1pdm09 - containing vaccine in a previous season and were vaccinated in the current season, the adjusted odds ratio was 7.7 with a confidence interval of 2.2 to 27.3. For women who did not receive a H1N1pdm09-containing vaccine in the previous season and were vaccinated in the current season, the adjusted odds ratio was 1.3 and was not statistically significant.

This study was subject to some limitations. The findings of effects of prior H1N1 vaccination were post-hoc secondary analyses. The study was not powered for the secondary analyses and although some relative risks were high, the confidence intervals were very wide. This is an observational study, which is subject to possible biases and confounding. It is possible that vaccinated women who had SABs were more likely to come to medical attention. It was not possible to include potential risks from influenza infection. There may be other unmeasured confounding factors as well.

The results of the VSD IIV3-SAB study suggest an increased risk of SAB in some pregnant women in the 1 to 28 days after receiving IIV3 during the combined 2010-2011 and 2011-2012 seasons. The risk was not increased in risk intervals more than 28 days after vaccination. An increased risk was observed in 2010-2011, but not in 2011-2012 when disregarding prior season vaccination with a H1N1pdm09-containing vaccine. In both seasons, increased risk was seen in women who had also received a H1N1pdm09-containing vaccine in the previous season, but not in women who did not receive a pH1N1-containing vaccine in the previous season.

It is important to note that these findings are preliminary and are inconsistent with prior research on IIV safety and pregnancy, including the prior VSD study and meta-analysis previously described. However, these studies did not evaluate the effect of prior vaccination. CDC plans to follow up on this finding for SAB following IIV3 with additional research in the VSD, and plans to replicate the study in more recent influenza seasons to assess the effect of prior vaccination with H1N1pdm09-containing vaccines as a primary objective. An attempt also will be made to evaluate the risk of SAB from influenza infection.

In conclusion, no new safety concerns during the 2014-2015 influenza season have been detected through VAERS surveillance. An elevated relative risk was detected in the VSD RCA for seizures following IIV3 and IIV4 in children aged 6 to 23 months. In terms of the VSD case-control study of SAB following IIV, the preliminary results from the 2010-2011 and 2011-2012 seasons show an increased risk of SAB following IIV3 among pregnant women in the 1- to 28-day risk window who had received a pH1N1-containing vaccine the prior influenza season. These findings are inconsistent with prior studies assessing IIV3 and SAB, and follow-up studies are planned.

Discussion Points

Noting that more than half of first-time miscarriages are associated with chromosomal abnormality, few patients accurately remember the date of their LMP, and especially first trimester ultrasounds are dependent upon the skill of the person doing them, Dr. Riley wondered what the mechanism would be to explain this finding.

Dr. Shimabukuro responded that the biological mechanism for this finding is unknown. In general, vaccination causes an inflammatory response. This is an observational, case-control study that is subject to the limitations mentioned. The investigators have performed a substantial number of sub-analyses to try to understand potential bias and confounding. The planned follow-up study will address the limitations mentioned.

Dr. Karron requested further information regarding the sub-analysis that was matched on LMP and all of the problems related to that, and the sub-analysis that assessed ultrasound-confirmed pregnancies as a subset in terms of future studies. She wondered about the utility of case-control studies versus cohort studies, given the difficulty in matching. While she recognized that cohort studies are larger and more expensive to conduct, perhaps it would be worth conducting further evaluation if there is believed to be a signal.

Dr. Shimabukuro replied that a sub-analysis was performed which was restricted to those cases with fetal cardiac activity. The result was that the odds ratios were still elevated. As mentioned in the methods, the SABs were from 5 to less than 20 weeks. That was also restricted to 7 to less than 20 weeks, and there was still an elevated odds ratio.

Dr. Donahue added that for the sub-analysis in which the study population was restricted to women who had an ultrasound in which fetal heart activity was detected, the question on the abstraction form was, "Is this a viable pregnancy?" The instructions to the reviewers were to look for fetal cardiac activity. Approximately 30% of the total cases reported fetal heart activity. As mentioned, it was not possible to repeat the analysis for effect modification because the numbers were not sufficient to do so. For the main effects model, the odds ratio actually increased. In respect to the study designs, there are some variations on the case-control design that might be beneficial in terms of offering some ability to control for individual factors. He agreed that the cohort design would be great, except that these do tend to be large, expensive, and subject to certain biases. One bias of major concern is the cases of miscarriage that occur that are not identified. There may be some association between the unidentified cases and the potential that they are more likely not to be vaccinated. Of course, any study conducted in a medical setting such as this is going to be subject to that type of bias.

Regarding the seizure study, Dr. Decker (Sanofi Pasteur) asked whether consideration had been given to an entry criterion of receipt of PCV, so that the entire population received PCV with or without another vaccine, which might or might not be IIV. He wondered whether an association was found with IIV that was, in effect, a modifier for the risk of seizure associated with PCV receipt. Or, if this was purely a situation in which because they were assessing IIV and some individuals received PCV and that causes seizures, there was an association with IIV. That is, is this like drunk driving after rum and Coke, where the Coke has little to do with it?

Dr. Shimabukuro responded that this is an RCA, so there is sequential monitoring during the influenza season. The particular methodology used was based on what was done during the 2010-2011 influenza season, during which they were assessing IIV and happened to have PCV13 surveillance underway at the same time. Thus, they were able to incorporate PCV13. The study was focused on IIV3 as the primary vaccine, along with other vaccines as well. He acknowledged that Dr. Decker's point was well-taken.

Dr. Frank DeStefano (ISO/CDC) said he thought ACIP had seen some data related to this about a year previously, which was presented by Jonathan Duffy. These analyses suggested that PCV vaccines had an independent effect which became stronger if they were concomitantly administered with IIV.

Dr. Gorman (NIH) pointed out that as CDC becomes increasingly proficient and all-encompassing with its surveillance, the numbers surveilled will be larger. Therefore, smaller and smaller differences will become statistically significant, making the job for ACIP increasingly harder. He recalled a previous presentation on the seizures that could be applied to spontaneous abortions as well, in which the number needed to vaccinate (NNV) to see that effect was presented. The NNV in a pediatrician's office presented as a data point would be useful in terms of whether they were talking about once a month, once a year, once every 10 years. Recalling the numbers from the last time the PCV-IIV data were presented, the average pediatrician would not see a seizure in his or her entire lifetime.

Dr. Temte noted that this was similar to the discussion years ago on MMRV, for which the level is dramatically similar at about 1 case per 2500.

Ms. Hayes (ACNM/ANA) asked whether Donahue et al. stratified the data based on when the vaccine was administered and when the loss occurred, emphasizing that a loss in pregnancy after 14 weeks usually has different causes. Between 14 and 20 weeks, there would be different risk factors than between 0 and 14 weeks of gestational age.

Dr. Donahue replied that they did not stratify because very few losses occurred beyond 13 weeks. The median gestational age for cases in this study was 7 and the peak was right around 7. There were not enough cases beyond 13 weeks to stratify the analysis.

It was not clear to Dr. Sawyer (PIDS) what practitioners should do regarding the statement on influenza vaccine and seizures. Under moderate problems reported, the advice is to "Tell your doctor if a child who is getting an influenza vaccine has ever had a seizure." Practitioners do not counsel to give separate vaccines or antipyretics.

Dr. Shimabukuro replied that what is placed on the VIS and the counseling that physicians offer are outside of the realm of the Immunization Safety Office (ISO).

Dr. Ault (ACOG) emphasized that many women in the case group were vaccinated within days of a missed period. Many women do not realize they are pregnant during this timeframe. Women who are vaccinated very early bias the study toward a low-risk group of controls and a high-risk group of subjects. He thought this explained most of the findings of this study.

Dr. Baker (IDSA) emphasized that little progress has been made with influenza vaccines in pregnant women since the pandemic, which relates to historical concerns. Now there are these data, with their limitations. She asked CDC's view and communication efforts regarding vaccination of women during the first trimester.

Dr. Schuchat replied that the pre-ACIP review of these data suggested that there was no need to change communication about influenza vaccine. This session's discussion was intended to focus on whether the signal merited further study for validation. A number of good comments were made regarding concerns about the validity of the study, which will inform the research plans. The limitations already raised suggested that the messages about influenza immunization during pregnancy do not need to be changed at this time. CDC has periodically revisited communication in the VIS rereading seizures relevant to influenza, MMRV, and PCV13. That will continue to be reviewed to ensure that the information is consistent and is communicated clearly for clinicians and consumers.

Recognizing that it might be a problem with small numbers, Dr. Temte asked whether any difference was observed when monovalent administration was followed by trivalent.

Dr. Shimabukuro responded that there was an effect modification for both seasons, so receipt of a monovalent over a trivalent was significant.

High-Dose Influenza Vaccine Update

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Dr. Grohskopf noted that as mentioned earlier in this session, the WG has had a number of discussions over the last several months regarding the use of high-dose and standard-dose influenza vaccines for older adults. While this is an ongoing discussion, the WG wanted to provide an update and invite comments from ACIP regarding how to proceed further.

In terms of background, high-dose inactivated influenza vaccine (HD-IIV) is only available as Fluzone® High-Dose from Sanofi Pasteur. It was approved in 2009. The basis for approval was superior immunogenicity compared with standard-dose inactivated influenza vaccine (SD-IIV) for persons greater than or equal to 65 years of age. A large randomized-controlled comparative trial was conducted over the 2011-2012 and 2012-2013 influenza seasons, which demonstrated a 24.2% better relative efficacy of HD-IIV versus SD-IIV for the prevention of laboratory-confirmed influenza associated with a protocol-defined influenza-like illness (ILI) among persons 65 years and older [DiazGranados CA, et al, N Engl J Med 2014; 371: 635-45]. Current ACIP recommendations state that either HD-IIV versus SD-IIV is an appropriate option for persons of this age group.

For this evaluation, the question assessed was: "Do benefits and harms favor HD-IIV versus SD-IIV for adults 65 years and older (i.e., better efficacy in preventing outcomes of interest; comparable safety profile)?" The population was adults 65 years of age and older. The intervention group was HD-IIV and the comparison group was SD-IIV. Because two vaccines were being compared head-to-head, the evaluation focused on head-to-head trials and abstracting data on each vaccine rather than placebo-controlled trials of one vaccine or another. Potential effectiveness and safety outcomes were generated by the influenza WG. Safety outcomes were further discussed with members of the Clinical Immunization Safety Assessment (CISA) Project for their input, and were ultimately rated in terms of perceived importance to policy-making decisions using a 1 to 9 scale, with 7 to 9 being critical, 4 to 6 being important, and 1 to 3 being considered not important for policy-making decisions. This was a somewhat more complicated analysis than was performed for LAIV, largely due to the fact that too many outcomes were included because several outcomes were interesting and relevant.

Regarding the efficacy analysis, the critical outcomes focused largely on laboratory-confirmed influenza (LCI) outcomes. For the purpose of the analyses, LCI meant that culture or PCR was used to confirm infection. The outcomes included any LCI from any virus or subtype, LCI-associated hospitalization, LCI-associated pneumonia, medically attended LCI or visits due to LCI, and LCI-associated emergency department visits. Important outcomes included medically attended acute respiratory illness (MAARI) and any ILI without regard to culture confirmation of the etiology.

Reviewing the literature for potential sources of efficacy and effectiveness data, five RCTs and one observational study were found. Further reviewing these studies, two papers were found that addressed the outcomes of interest: 1) DiazGranados 2014, which was a very large study of over 30,000 enrollees; and 2) DiazGranados 2013, which was the precursor of the 2014 study. The 2013 study was a very similar design, was initiated during the 2009-2010 season, and was intended to be a multi-year study. But the pandemic came about during 2009, which made it difficult to assess seasonal influenza vaccine VE. Therefore, the 2013 study was stopped and a similar study began again, which became DiazGranados 2014. Of note, there was no information for a number of outcomes that were also considered either critical or important. No studies addressed LCI-associated deaths or a number of other important outcomes focused primarily on the impact of influenza on independence and the ability to maintain activities of daily living among the elderly.

In terms of efficacy outcomes, there was a significant difference favoring HD-IIV. The critical outcome of LCI (all viral types and subtypes) was assessed two ways. Both analyses used DiazGranados 2013 and 2014 reported LCI influenza outcomes. Because DiazGranados 2013 occurred at the beginning of the pandemic, it might be argued that it is not fair to include it. It could be anticipated that a seasonal vaccine would not cover a relatively antigenically novel pandemic strain. When both RCTs were included in the analysis and no parameters were downgraded, the overall evidence was Type 1 (high) with a risk difference of 0.82 and a 95% confidence interval of 0.71 to 0.95. When DiazGranados 2013 was removed, those numbers remained the same. The risk difference changed very slightly. In the assessment for the individual studies, the weight of DiazGranados 2013 was lower. It was a smaller study with fewer overall events reported. At least in analyzing in this manner, the risk ratio and confidence interval were similar regardless of whether DiazGranados 2013 was included.

For the other critical outcomes (LCI-associated hospitalizations, LCI-associated pneumonia, medically attended LCI, and LCI-associated emergency department visits), the only data available were from DiazGranados 2014 that were reported in the supplementary material published with the *New England Journal of Medicine* (*NEJM*) article. This analysis was downgraded for indirectness, given that the events were reported as any such event that occurred within a 30-day period after the LCI. Particularly for hospitalization and emergency department (ED) visits within this age group, the WG considered the possibility that these diagnoses or events were not necessarily related to influenza or the index illness at that time period. This analysis was also downgraded for imprecision, given that the confidence intervals were fairly wide and that the criteria were met in only three out of four cases. Only medically attended LCI was not downgraded for imprecision. The overall evidence types were Type 3 (low) for hospitalization, pneumonia, and ED visits; and Type 2 (moderate) for medically attended or medical visits due to LCI. In no case was the difference significant.

Critical safety outcomes included AE causing study discontinuation and any related SAE. Important outcomes included any SAE, any death, fever (any grade), myalgia (grade ≥2), headache (grade ≥2), malaise or fatigue (grade ≥2), local swelling/induration (grade ≥2), and local pain (grade ≥2). For this analysis, there were more data sources for most of the outcomes. In a review of literature, 7 RCTs were found that provided some degree of safety data. The important outcomes of fever, myalgia, headache, malaise or fatigue, local swelling / induration, and pain were largely reported by two studies: Couch 2007 and Falsey 2009. Falsey is regarded as the pivotal safety study for HD-IIV versus SD-IIV. Symptomatic AEs were reported by Keitel 2006, although some of them were reported in a way that made abstracting the individual symptoms difficult. The WG will return to this when this assessment is performed again.

For the critical safety outcomes (AE causing study discontinuation, any related SAE, and immediate hypersensitivity or anaphylaxis), some studies reported an event count of 0 and did not contribute to risk calculations. Immediate hypersensitivity / anaphylaxis was not reported for any study. AE causing study discontinuation and any related SAE were downgraded for imprecision because the 95% confidence interval included 1.0 and exceeded 0.75 in the lower bound and/or 1.25 in the upper bound, for an overall quality of evidence of Type 2 (moderate). There was no significant difference between AE causing study discontinuation or any related SAE between the two vaccine groups. There was a significant amount of discussion with the CISA Project and the WG regarding immediate hypersensitivity or anaphylaxis. There was general consensus that had these events occurred, they would have been reported. Assuming that was the case, there would have been zeros in all cells and none of the parameters could have been calculated for risk difference or relative risk. While it may be possible to acquire more information in the future, this is about as much as can be said at this time.

As originally conceptualized, deaths were not stratified by time. However, because some of the papers stratified in this way, the decision was made to divide the important safety outcomes into three groups (any SAE without regard to relatedness, any death within 6 months, or any death within 30 days) and present the results this way. Death within six months was downgraded for an imprecise / wide confidence interval. Any death within 30 days with an extremely wide confidence interval was downgraded, and the outcome of any SAE was not downgraded. Unfortunately, any SAE is a general outcome and it was not possible to confirm whether those were due to influenza. Most likely, they were not. In many trials, SAEs are not due to the intervention. However, it was one of the few interventions with which they could try to capture potentially bad events that may be associated. There were 7 studies that contributed to this analysis. The overall evidence was Type 1 (high) for any SAE, Type 2 (moderate) for death within 6 months, Type 3 (low) and for death within 30 days. In any condition for all three of these, there were no significant differences in the pooled relative risk between the two vaccines.

No significant difference was observed for the important outcomes of fever of any grade or myalgia $\geq$2. Only imprecision was downgraded, for an overall evidence of Type 2 (moderate). There was a significant difference in moderate to severe headache and moderate to severe malaise or fatigue, both on the order of a relative risk of about 1.5. No features were downgraded for these outcomes, and the overall evidence was Type 1 (high). Each of these outcomes was addressed by Falsey et al. (the pivotal safety study mentioned earlier) and the smaller Couch study. Anecdotally, the grade 3 only observations were also considered for each of these outcomes and observed a strong association for myalgia and a slightly stronger association for the other two outcomes. However, doing so eliminates Couch and leaves only one study from one season.

In terms of the important outcome of local swelling or induration of grade ≥2, a significant difference was observed in local swelling or induration and no parameters were downgraded. Both studies addressed this outcome. A significant difference was not observed for local pain or tenderness of grade ≥2. This outcome was downgraded for the wide confidence interval. The overall evidence was Type 2 (moderate).

Event counts for Couch 2007 were fewer, so that study was weighted less. When the analyses were restricted to grade 3 events only, Couch generally had zero events in each cell and fell out. It was not that Couch did not report these events. It was just that the events did not occur. This resulted in a pooled relative risk, which was really a pool of one study. Similarly, for malaise or fatigue of grade 2 or higher for which there was a significant difference of 1.5, Couch reported some symptoms. Local swelling or induration with a pooled ratio of 1.6 was also significant.

To summarize critical outcome results, there was a difference that favored high-dose vaccine for prevention of laboratory-confirmed influenza with high quality evidence. There was no difference and low to moderate quality evidence in the findings for the efficacy / effectiveness outcomes of LCI-associated hospitalization, LCI-associated pneumonia, medically attended LCI, or LCI-associated ED visits; or the safety outcomes of SAEs causing study discontinuation or any related SAE. There is no information on deaths. The overall quality of evidence for this assessment was deemed to be Type 3 (low).

There are a number of limitations to this analysis. The main source for efficacy outcomes is a single study conducted over two seasons. Having two seasons is good in that influenza varies from season-to-season in terms of vaccine effectiveness and reactogenicity. Outcomes could be impacted as well by not having more than one season represented. Data were not available for a number of critical outcomes (LCI-associated deaths, anaphylaxis), or available data were indirect (LCI-associated severe clinical outcomes). However, it is potentially difficult to power a RCT for these outcomes. Hospitalizations may be difficult as well, possibly requiring a large observational study. Some of the safety outcomes of interest are very uncommon, again making it difficult to power for some of these outcomes. In addition, safety outcomes may not have been defined or interpreted similarly across studies. Though fever was defined relatively uniformly, swelling was not. This resulted in the need to make some assumptions.

It is important to note that an additional study was found but not included in the GRADE analyses [Izurieta HS, et al, Lancet Infect Dis, online February 9, 2015]. This was a retrospective cohort study of Medicare beneficiaries 65 years of age and older who received HD-IIV or SD-IIV during the 2012-2013 influenza season. The primary outcome was probable influenza infection based on receipt of a rapid influenza test followed by dispensing of oseltamivir. The secondary outcome was a hospital or ED visit listing a Medicare billing code for influenza. Among 929,730 HD-IIV recipients and 1,615,545 SD-IIV recipients identified, HD-IIV was 22% (95%CI 15-29) more effective in preventing probable influenza; and 22% (95%CI 16-27) more effective in preventing influenza hospital admission. However, this study was not included in GRADE it did not address critical / important outcomes selected by the WG, and that it would have been somewhat of a stretch to call this LCI. As an observational study, it would have started out as Type 3 evidence, which already would have been low. The study likely would have had to be downgraded simply because, at minimum, it did not address a direct outcome.

Also important to note is that VAERS is constantly collecting safety data. A paper was published by Moro et al. based on VAERS data for the 2010-2011 influenza season, which analyzed events associated with HD-IIV. There were 606 reports in patients 65 years of age or older. Only 8.2% of these events were judged as serious, which is reassuring. MedDRA terms for ocular hyperemia and vomiting exceeded the data-mining threshold during that period. Of these reports, 80% were non-serious, which also is reassuring. Clinical review of serious reports found a greater proportion of gastrointestinal events compared to IIV3 standard dose. During the first year after US licensure of trivalent, inactivated influenza vaccine (TIV-HD), no

new serious safety concerns were identified in VAERS. Analyses suggested a clinically important imbalance between the reported and expected number of gastrointestinal events after IIV3-HD receipt [Moro et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clin Infect Dis. 2012;54(11):1608-14].

Regarding Fluzone High-Dose® post-licensure safety data from 2011-2015, between 2011 and 2015 disproportional reporting for the MedDRA term "vomiting" was observed during the 2012 and 2013 season. Most vomiting reports were non-serious and self-limited. There also was disproportional reporting for the MedDRA term "drug administered to patient of inappropriate age," which is more of an error than an AE. No new safety concerns were identified in VAERS reporting for Fluzone High-Dose® in monitoring from 2011-2015 following its initial season of use.

The WG does have a continuing interest in populations who are vulnerable to more severe outcomes. However, the WG does not think there is consensus at this time that alternative policy language or preferential language should be proposed based on the available evidence. The WG will consider further evaluation as more data become available. They are aware of at least one other study that is being conducted currently in elderly nursing home patients, for which the data are not anticipated to be available for at least another year.

Discussion Points

Dr. Greenberg (Sanofi Pasteur) noted that Sanofi Pasteur looks forward to ongoing discussions. They have been performing more analyses on the data available from the seminal trial. He agreed with the conclusion that it did not make sense to include the data from the 2009-2010 season in GRADE since the strain was not in either HD-IIV or SD-IIV. Regarding the primary study, he noted that the 24.2% relative efficacy reduction of disease noted in this presentation was the primary endpoint of the study. Based on the presentation, it appeared that relative efficacy for any laboratory-confirmed respiratory illness was used. That was a less sensitive or less severe case in the sense that respiratory illness of that study was defined as "any one respiratory symptom." Sneezing alone would qualify for a respiratory infection; whereas, the protocol-defined ILI was at least one systemic symptom and one respiratory symptom. Publications are anticipated in the summer and fall that pertain to some of the secondary analyses and cost-effectiveness. Sanofi Pasteur looks forward to sharing those data with the WG. At 24% relative efficacy, there is a substantial cost savings because of reduced influenza-related hospitalizations. He thinks that is an important or critical endpoint the WG will want to consider.

Dr. Grohskopf replied that the WG did use the respiratory illness definition in the hope of capturing as large a number of cases as possible. They did consider the other definitions as well, because that paper lays out the results for the different definitions of respiratory illness used.

Dr. Decker (Sanofi Pasteur) reminded everyone that influenza-related deaths in the over-65 population is 1% annually. Therefore, anything that might be influenza-specific is swamped by other numbers. That is why it is very difficult to exact anything at all for that particular parameter. Regarding the Izurieta study, he recognized that GRADE has rules and that the study is observational, is not laboratory-confirmed, et cetera. However, this is a major CDC / FDA / CMS study with over 2 million subjects evaluated. A primary outcome of this study was a 22% statistically significant reduction in the rate of hospitalization. To say, "Well, it's outside of

our rules" when it is CDC's own study seemed a little strange. He noted that the nursing home study is also observational, so while waiting for it, they should review Izurieta again.

Dr. Grohskopf emphasized that there is absolutely no prohibition against using observational studies, and they would like to see more of them. In fact, observational data were used in the last assessment of LAIV vs IIV for young children. It was more an issue of trying to walk the balance between what are believed to be the most important outcomes. In the past, there has been a lot of discussion regarding the use of more specific outcomes for influenza vaccine. For example, rather than using serologic data, perhaps using hard endpoints associated with lab-confirmed disease. CDC and the WG believe the Izurieta study to be important, which is why they raised it for discussion. It did not quite fit within GRADE. Had it been used in the GRADE analysis, it probably would have lowered the quality of evidence because they would have to have downgraded it. They would like to include more observational studies, and will continue to search for them.

Proposed Recommendations

Lisa A. Grohskopf, MD, MPH
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

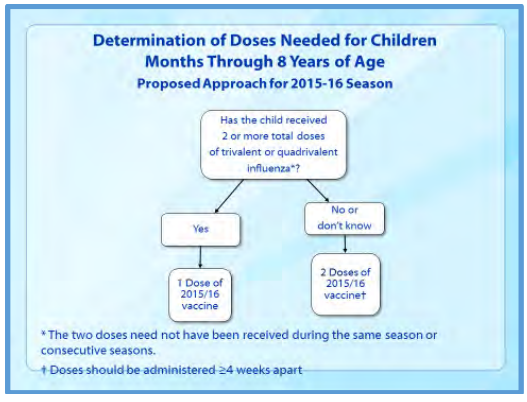
Dr. Grohskopf first recapped what occurred during the truncated February 2015 ACIP meeting. As is typical in February of each year, the core guidance was reiterated that annual, routine influenza vaccination is recommended for all persons aged 6 months and older. That was approved and was signed off on the Internal Decision Memo, as was the revision of the recommendations regarding use of LAIV for healthy children 2 through 8 years of age and that for the next season, no preference is expressed for LAIV or IIV for any person aged 2 through 49 years for whom either vaccine is otherwise appropriate. Further proposed updates for 2015-2016 included the US influenza vaccine composition for 2015-2016 (there are a couple of strain changes, so that will be mentioned); updated influenza vaccine product descriptions, reflecting new licensures, labeling information, and expected availability; and a revised algorithm for determining the number of doses needed for children 6 months through 8 years of age.

For information and not a vote, there is a strain change in the vaccine composition for 2015-2016. The H1N1 virus will be the same A/California/7/2009-like virus, which is the (H1N1)pdm09 type virus. That has been in the seasonal vaccine since 2010-2011. There will be a new H3N2 strain, A/Switzerland/9715293/2013 (H3N2)-like, which replaces A/Texas/50/2012-like viruses. For B strains, the B/Phuket/3073/2013-like virus, which is a Yamagata lineage virus, will replace the B/Massachusetts/2/2012-like virus, which is a different Yamagata lineage virus. For the quadrivalent vaccines, these viruses will be present plus a B/Brisbane/60/2008-like virus (Victoria lineage). That was also the second B virus recommended for last season, so that is not a change.

New licensures, labeling information, and expected presentations reflected in text and/or table for influenza vaccine product updates for 2015-2016 will include the following:

- ❑ Fluzone® Intradermal Quadrivalent IIV
- ❑ Expanded age indication for Flublok® (now 18 and older), which was previously noted in the online vaccine table and the ACIP Adult Schedule
- ❑ Approval of administration of Afluria® by Stratis® jet injector for persons 18 through 64 years of age, which was previously noted in the online vaccine table
- ❑ Any additional labeling changes arising prior to publication

Regarding determination of doses needed for children months through 8 years of age, since 2010-2011, the algorithm for determining the appropriate number of doses in this age group has considered vaccine doses containing A(H1N1)pdm09 separately. As a pandemic virus, it is considered to be relatively antigenically novel. This led to somewhat complicated algorithms. This virus has been represented by an A/California/7/2009 (H1N1)-like virus in trivalent and quadrivalent vaccines since 2010-2011. There is likely a diminishing number of children each season who have not been exposed to this virus. The WG proposed language that would eliminate separate counting of doses containing A(H1N1)pdm09-type virus in order to have a single simplified algorithm as depicted in the following graphic:



Discussion Points

Dr. Schuchat asked whether "tri" or "quad" could be crossed out.

Dr. Grohskopf replied that "trivalent" and "quadrivalent" were included so that monovalent vaccine doses would not be counted as one of the two previous doses. If a child received one dose of seasonal and one dose of monovalent pandemic vaccine, that child should receive two doses.

Dr. Kimberlin (AAP) said he personally liked having trivalent or quadrivalent simply because practitioners will think about it.

Dr. Kempe asked if the WG discussed clarifying that it need not be concurrent seasons, given the potential for confusion.

Dr. Grohskopf noted that this was the reason for the addition of the footnote, and that the text also discusses that the doses do not need to be administered during the same season. She suggested stating that "The two doses do not need to have been received during the same season or consecutive seasons."

Dr. Belongia suggested asking "Has the child previously received two or more total doses of trivalent or quadrivalent influenza vaccine?" and keeping the footnote.

Dr. Hahn (CTSE) expressed concern regarding removing the wording about prior seasons. A child who already received an influenza vaccine in that season may still be interpreted as needing another dose. She suggested removing the word "any" since it made it seem like only one season and asking, "Has a child received two or more total doses during prior seasons?"

Dr. Grohskopf said the more she thought about it, what made the most sense was to remove "any prior seasons" to have the question read "Has the child previously received two or more total doses of trivalent or quadrivalent influenza vaccine?" and add to the footnote that they do not have to have been in consecutive seasons.

Dr. Loehr (AAFP) pointed out that one problem would be if someone received a dose in September 2015 as well as during the previous year, and thought they did not need another dose in October.

Dr. Grohskopf acknowledged that this would be counting across the current upcoming season and the last season. She suggested that a simple fix might be in the last two boxes where the number of doses are specified to state "of 2015-2016 influenza vaccine" to specify the current season. She clarified that the language would be "Has the child previously received two or more total doses of quadrivalent or trivalent influenza vaccine? If yes, one dose of 2015-2016 influenza vaccine. If no or don't know, two doses of 2015-2016 influenza vaccine." The footnote would be amended to state, "The two doses need not have been received during the same season or consecutive seasons."

Dr. Temte clarified that the motion and vote would be for the language change proposed for the 2015-2016 influenza season recommendation for the number of doses for children 6 months through 8 years of age and to affirm the vaccine components and product updates.

Vote: 2015-2016 Influenza Season Recommendation Language Revision for Number of Doses for Children 6 Months through 8 Years of Age and Affirmation of Vaccine Components and Product Updates

Dr. Kempe made a motion to for the language revision proposed to the recommendation for the doses needed for children 6 months through 8 years of age for the 2015-2016 influenza season, and to affirm the components of the 2015-2016 vaccine components and product updates. Ms. Pellegrini seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

14 Favored:	Bennett, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed:	N/A
1 Abstained:	Belongia

Smallpox Vaccine

Introduction

Lee Harrison, MD
ACIP, Work Group Chair

Dr. Harrison reminded everyone that numerous occurences of laboratory-acquired orthopoxviruses infections have been reported. The current smallpox vaccine provides cross-protection against all orthopoxviruses that cause infections in humans (e.g., smallpox, monkeypox, vaccinia, and cowpox). Smallpox vaccine is currently used to protect clinical and research laboratory workers against these viruses. He shared several images of ocular, ear, and needlestick vaccinia virus transmissions in laboratory workers and smallpox vaccination complications. The types of complications shown generally do not occur with the type of screening currently utilized to exclude persons with contraindications prior to immunization.

Regarding vaccination versus laboratory infections, with vaccination there is a well-formulated virus in a dosage delivered through a controlled route at a location that minimizes risk of spread. In terms of laboratory infection, a variety of strains are being used with unknown pathogenic potential, there may be high titers of virus, and transmission may occur through an unusual route (e.g., deep injection, atypical site on body, ocular exposure) [Source: Mary Reynolds].

In terms of background, ACIP recommendations for smallpox vaccination of laboratory workers have not been updated since 2003. A new smallpox vaccine, ACAM2000™, was licensed in 2007 and has replaced the previously used smallpox vaccine, Dryvax®. The Smallpox Vaccine Work group was established in March 2013, and monthly meetings have been held since that time. This has been a very productive group, which has engaged in detailed discussions and provided significant input.

The work group's terms of reference are as follows:

1. Review recommendations for smallpox vaccination for lab workers in 2001 statement (and supplements from 2003):

    a. Review Biosafety in Microbiological and Biomedical Laboratories (BMBL) requirements for work with orthopoxviruses
    b. Review orthopoxvirus laboratory exposure cases and reports

2. Review data on smallpox vaccine:

    a. ACAM2000™
        - Safety and immunogenicity data
        - Adverse event rates with current stringent prescreening program
    b. Dryvax: Publications on 2002 through 2004 pre-event smallpox vaccination program

3. Review human safety and animal model efficacy data for attenuated smallpox vaccine IMVAMUNE stored in Strategic National Stockpile and potential role in smallpox vaccination for lab workers (unlicensed product and therefore informational).

4. Review data on recombinant vaccinia viruses in development or under investigation in clinical trials to provide guidance on need for smallpox vaccination in healthcare and/or laboratory personnel working with these viruses.

5. Revise existing statement and supplements for smallpox vaccination of laboratory workers into single ACIP Policy Note document.

Proposed Smallpox Vaccine Recommendations

Brett W. Petersen, MD, MPH
Medical Officer, Poxvirus and Rabies Branch, CDC
Lieutenant Commander, U.S. Public Health Service

Dr. Petersen indicated that with regard to background, orthopoxviruses are a group of large double-stranded DNA viruses within the family *Poxviridae*. There are four known species that infect humans: Variola (Smallpox), Vaccinia (Smallpox Vaccine), Monkeypox, and Cowpox. Orthopoxvirus virus infections provide cross-protection across species. It is this property that allowed the development of vaccinia as a vaccine for smallpox and other orthopoxviruses and has ultimately resulted in eradication of smallpox as a human disease. However, orthopoxviruses remain an active subject of research.

In particular, vaccinia viruses are commonly used in laboratory research. There are many historic vaccine seed stocks and derivatives including the following: New York City Board of Health (NYCBH), Lister, Modified Vaccinia Ankara (MVA), Western Reserve, LC16M8, Copenhagen, among others. Different vaccinia viruses demonstrated varying degrees of attenuation and safety profiles. Recombinant vaccinia viruses are being used increasingly in the laboratory setting as viral vectors for expression of foreign genes using gene therapy or genetic engineering, and are also under investigation as potential recombinant vaccines and as oncolytic or immunotherapy for cancer.

Vaccinia virus smallpox vaccines have been recommended by ACIP for the protection of laboratory workers against orthopoxvirus disease since 1980. ACIP last produced recommendations for vaccinia vaccine for laboratory workers in 2001. At that time, ACIP recommended vaccinia vaccine for laboratory workers who directly handle cultures or animals contaminated or infected with non-highly attenuated vaccinia virus, recombinant vaccinia viruses derived from non-highly attenuated vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, vaccinia, and variola). Vaccination can be offered to healthcare workers with direct contact with dressings or other infectious material from volunteers in clinical studies where non-highly attenuated vaccinia viruses or recombinant viruses derived from these strains are used. Laboratory and healthcare personnel working with highly attenuated poxvirus strains do not require routine vaccinia vaccination. Highly attenuated poxvirus strains include the following:

- MVA: Derived from vaccinia virus Ankara
- NYVAC: Derived from vaccinia virus Copenhagen
- TROVAC: Derived from fowlpox virus
- ALVAC: Derived from canarypox virus

ACAM2000™ is currently the only smallpox vaccine licensed and available in the US. It was licensed in 2007 and replaced the previously used smallpox vaccine, Dryvax, which was referred to in the previous ACIP recommendations and is no longer available. ACAM2000™ has been used in laboratory and healthcare workers and select DoD personnel. It is a live vaccinia virus vaccine that is produced in vero cells. It is derived from a clonal isolate of Dryvax, a New York City Board of Health strain used during the smallpox eradication campaign. ACAM2000™ is administered in a single dose percutaneously via multiple puncture with a bifurcated needle. Following vaccine administration, a lesion develops at the site of vaccination. During this time, the lesion does contain infectious virus that can be transmitted to others via inadvertent inoculation or to other sites of the body via auto-inoculation. However, this cutaneous response is also referred to as a "take" and is considered a marker of successful vaccination.

Historically, smallpox vaccines have been associated with a number of adverse events, some of which can be severe and life-threatening. Some of those include eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis. Based on data from primary vaccination with Dryvax® from a study conducted in 1968 during the time of routine immunization with smallpox vaccine, the rates ranged from 1.5 cases/million vaccinations to 38.5 cases/million vaccinations. Overall rates for deaths were also reported as approximately 1 death/million vaccinations. The rates for revaccination were much lower than those for primary vaccination [Adapted from Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys, J Infect Dis. 1970 Oct;122(4):303-9 and ACAM2000™ package insert].

Based on data from a more recent study evaluating the adverse event rates observed during the DoD and HHS vaccination programs during 2002 and 2005, of note was the absence of any observed eczema vaccinatum or progressive vaccinia cases. This was likely due to the stringent screening of persons for risk factors for these adverse events. Also of note was the identification of myo/pericarditis, which had not previously been recognized as a significant adverse event related to smallpox vaccine [Adapted from Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. Vaccine 2005, Mar 18;23(17-18):2078-81 and ACAM2000™ package insert].

Using this background, the WG used the GRADE methodology to assess the ACAM2000™ in laboratory workers utilizing the following steps:

- ❑ Development of a policy question
- ❑ Identification and assessment of the importance of outcomes
- ❑ Review of the literature
- ❑ Summarization of the evidence for critical outcomes
- ❑ Evaluation of the quality of evidence for outcomes

The policy question formulated by the WG was, "Should administration of ACAM2000™ be recommended routinely to persons at risk for occupational exposure to orthopoxviruses?" The population of interest was persons at risk for exposure to orthopoxviruses. The intervention was vaccination with ACAM2000™, the currently available vaccine, and the comparison was vaccination with the previously recommended vaccine, Dryvax. A modified Delphi method was used to solicit outcomes assessments from the WG members. The outcomes identified included benefits and harms. Among the benefits were vaccine efficacy to prevent orthopoxviral disease, cutaneous response or take, and neutralizing antibody response.

Among the harms were serious adverse events, myo/pericarditis resolved with sequelae, myo/pericarditis resolved without sequelae, inadvertent inoculation, and mild adverse events. Outcomes deemed to be critical were vaccine efficacy to prevent orthopoxviral disease, serious adverse events, and myo/pericarditis resolved with sequelae. All of the outcomes were assessed to be important and all were eventually included in the final evidence profile.

A systematic literature review was performed to identify studies that met the criteria and addressed the outcomes identified by the work group. A total of 5 RCTs were identified that addressed the benefits outcomes, 4 of which also addressed the harms outcomes. Cutaneous response was best assessed in two studies evaluating this outcome in vaccinia-naïve and previously vaccinated subjects who were vaccinated with both ACAM2000™ and the comparator Dryvax. Of vaccinia-naïve subjects receiving ACAM2000™, 96% demonstrated vaccination success. ACAM2000™ was found to be non-inferior to the comparator, Dryvax, among this population. Of the previously vaccinated subjects receiving ACAM2000™, 84% demonstrated vaccination success by cutaneous response as compared to 98% of Dryvax® subjects. A statistical analysis revealed that ACAM2000™ did not meet the predefined criteria for non-inferiority to Dryvax® among this population. In terms of the neutralizing antibody response, these same studies evaluated the response in both vaccine-naïve and previously vaccinated subjects. Among vaccinia-naïve subjects, the geometric mean neutralizing antibody titer and the Log_{10} mean were comparable to the comparator, Dryvax, although by the slightest of margins ACAM2000™ did not meet the criteria for non-inferiority to the comparator vaccine. In contrast, among the previously vaccinated subjects, the neutralizing antibody titers were again similar and in this instance did meet the criteria for non-inferiority.

Regarding the critical harms outcomes, no serious adverse events were reported in the RCTs reviewed (e.g., death, eczema vaccinatum, progressive vaccinia, or postvaccinial encephalitis). There were 7 cases of suspected myo/pericarditis reported among the 2983 clinical trial participants who received ACAM2000™. The best estimate of risk based on detection of 5 cases among 873 vaccinees during Phase 3 clinical trials incorporating active monitoring for myocarditis and pericarditis is 5.7 cases/1000 vaccinees. Two cases among those reporting myo/pericarditis demonstrated sequelae (e.g., persistent abnormal echocardiogram at one year). All cases of myo/pericarditis in these clinical trials did resolve.

Using the GRADE methodology to assess the evidence, the WG had no concerns for risk of bias or inconsistency for any of the outcomes. However, concerns about indirectness and imprecision were identified as issues for several outcomes and the evidence type was downgraded accordingly. Three outcomes were downgraded for indirectness, because the outcome that was assessed differed from those of primary interest. Cutaneous response and neutralizing antibody response were used as surrogates for the outcome of primary interest, which was vaccine efficacy to prevent orthopoxviral disease. No data were available for this primary outcome. The clinical significance of myo/pericarditis, which resolved without sequelae, is unclear. Many of these cases were asymptomatic disease that were only detected due to the intensive cardiac monitoring that participants underwent, including routine EKGs and cardiac enzyme evaluation. For this reason, myo/pericarditis that resolved with sequelae was felt to better represent the outcome of primary interest.

Regarding imprecision, the work group found that the clinical trials were not adequately powered to detect serious adverse events (e.g., death, eczema vaccinatum, progressive vaccinia, or postvaccinial encephalitis), and were not powered to detect inadvertent inoculation. Calculations of the probability that these adverse events would not be observed based on the number of participants in the clinical trials, as well as the sample size that would be needed to

detect these events, support the assessment of imprecision in these cases. Based on this GRADE assessment, the overall level of evidence was determined to be 2, which is consistent with RCTs with important limitations.

The WG also considered the risk of exposure and infection in developing the proposed recommendations, and found that these risks are very difficult to quantify. The population at risk is difficult to estimate, given that there is no registry of persons who work with orthopoxviruses. The WG also assessed indirect measures that offer some sense of the size of this population, including the following:

- 431 orthopoxvirus-related publications in 2013 on PubMed (361 with "vaccinia" in title or abstract, 34 "monkeypox," 36 "cowpox")
- 185 active projects listed on NIH Research Portfolio Online Reporting Tools at http://projectreporter.nih.gov/
- 25 open clinical trials involving vaccinia virus listed on NIH's clinicaltrials.gov
- 31 different sites received 80 shipments of smallpox vaccine from CDC in 2013 (96 different sites received 523 shipments during 2009–2013)

The risk of orthopoxviral disease is difficult to estimate as well, given that surveillance is not ideal and the true burden of disease is not known. Vaccinia and cowpox infections are not reportable conditions, so there is not a comprehensive list of all potential infections. Similarly, orthopoxvirus exposures are not always reported. In addition, the pathogenicity and virulence of the virus may not be well-characterized, particularly with regard to recombinant viruses. However, CDC maintains a database of laboratory-related orthopoxvirus exposures and infections that have been reported since 2004. Of the 26 exposure incidents reported, 18 (69%) involved recombinant viruses and 14 (54%) resulted in infections. Of those 14, 12 (86%) involved recombinant viruses, 12 (86%) involved vaccinia infections, 2 (14%) involved cowpox infections, 4 (29%) required hospitalization, and 4 (29%) involved infection with a strain other than that with which they were working (or thought they were working). Of the 26 exposure incidents reported, 7 (27%) met ACIP vaccination recommendations, and 1 of those 7 (14%) resulted in infection. One other infection occurred in an individual vaccinated over 10 years prior, which did not meet the ACIP vaccine recommendations for revaccination.

In terms of conclusions and recommendations, the WG concluded that ACAM2000™ is comparable to Dryvax® in providing protection against orthopoxviruses, with an overall evidence Type 2. The WG proposed extending the current ACIP recommendations for use of smallpox vaccine among laboratory and healthcare workers at risk for occupational exposure to orthopoxviruses. The proposed recommendations presented for a vote follow:

- Routine vaccination with ACAM2000™ is recommended for laboratory workers who directly handle a) cultures or b) animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, and variola) (recommendation category: A, evidence type 2).

- Vaccination with ACAM2000™ is not recommended for persons who work only with replication-deficient strains of vaccinia virus (e.g., MVA, NYVAC, TROVAC, and ALVAC) (recommendation category: A, evidence type 2).

- ❑ Health-care workers (e.g., physicians and nurses) whose contact with replication-competent vaccinia viruses is limited to contaminated materials (e.g., dressings) and persons administering ACAM2000™ smallpox vaccine who adhere to appropriate infection prevention measures can be offered vaccination with ACAM2000™ (recommendation category: B, evidence type 2).

The WG proposed that contraindications remain in place, with two exceptions: 1) the addition of a contraindication for persons with a household contact less than one year of age, given that this population is at increased risk of SAEs, particularly postvaccinial encephalitis; and 2) the removal of the contraindication for revaccination of persons who have three or more known major cardiac risk factors, given that myo/pericarditis was not observed in clinical trial participants who were undergoing revaccination and was only seen in primary vaccinees:

Proposed Recommendations

Contraindication	Primary Vaccinees	Revaccinees	Household Contacts*
History or presence of atopic dermatitis	X	X	X
Other active exfoliative skin conditions†	X	X	X
Conditions associated with immunosuppression§	X	X	X
Pregnancy	X	X	X
Aged <1 year¶	X	X	X
Breastfeeding	X	X	
Serious vaccine component allergy	X	X	
Known underlying heart disease	X	X	
≥ 3 known major cardiac risk factors**	X		

* Household contacts include persons with prolonged, intimate contact with the potential vaccinee (e.g. sexual contacts) and others who might have direct contact with the vaccination site.
† Conditions include eczema, burns, impetigo, varicella zoster, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease keratosis follicularis.
§ Conditions include HIV/AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplantation, or therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor (TNF) inhibitors, or high-dose corticosteroids; hematopoietic stem cell transplant recipients <24 months post transplant or ≥24 months, but have graft-versus-host disease or disease relapse, or autoimmune disease with immunodeficiency as a clinical component.
¶ Vaccination of infants aged <1 year is contraindicated. Additionally, the Advisory Committee on Immunization Practices does not recommend vaccinating children and adolescents aged ≥16 years.
** Major cardiac risk factors include hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking.

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The WG was not unanimous. One WG member submitted the following dissenting view on the level of recommendation for workers handling vaccinia virus, as well as alternative language:

- ❑ The risk-benefit ratio for routine smallpox vaccination of laboratory workers handling vaccinia virus has changed significantly:
  - As opposed to the ACIP recommendations in 1980, today vaccination of most workers is no longer a boost vaccination, but a primary vaccination that carries more risk.
  - This change in risk likely should have been addressed in 2001 when the recommendations were revised.
  - This change in risk at least needs to be acknowledged.

- ❑ How can the level of evidence and the risk/benefit ratio for lab workers handling vaccinia virus be the same as for those working with variola and monkeypox viruses?
  - Variola and monkeypox would cause a more serious infection after a lab accident and have public health implications. Thus there is an acceptable risk-benefit ratio when recommending routine vaccination for these viruses.
  - The same cannot be said for those working with vaccinia virus.

- ❑ Therefore, the strength of recommendation for all workers handling vaccinia virus needs to be adjusted.

Suggested alternative language is as follows:

- A careful assessment of the type of work being done with vaccinia virus should be made and those at high risk of an accidental exposure should be vaccinated.

- Alternatively, as opposed to "recommendation category: A, evidence type 2" a lower level should be assigned to the recommendation to vaccinate workers who handle vaccinia virus:
    - An argument can be made for a lower recommendation category since it is difficult to quantify the risk of occupational exposure to vaccinia virus

There did seem to be general consensus among the WG for a Category A recommendation for persons working with vaccinia virus to be vaccinated with ACAM2000™ vaccine. After multiple reviews of the language and the Policy Note, Dr. Petersen did not receive any individual input from other WG members suggesting that this should be anything other than a Category A recommendation.

Discussion Points

Dr. Belongia requested additional information about current DoD policy and recent DoD experience with the use of ACAM2000™ vaccine, and whether there are any more recent safety data from DoD than 2005.

Dr. Petersen replied that in general, the DoD recommendations and contraindications essentially align with ACIP recommendations. The exception would be the proposed changes to the ACIP contraindications. In terms of safety data, the WG heard a presentation from the DoD that did not identify any new safety signals in the ongoing DoD smallpox vaccination program.

Dr. Campos-Outcalt asked how many members of the DoD are being vaccinated currently.

Dr. Petersen responded that the DoD is still vaccinating a small number of individuals who are being deployed.

Dr. Sergienko (DoD) added that the DoD is still vaccinating people who are going into areas where there is concern for potential high-risk. The safety profile has not changed.

Dr. Campos-Outcalt observed that the first bullet in slide 26 stated that, "ACAM2000™ is comparable to Dryvax® in providing protection against orthopoxviruses (Overall evidence type 2)," but it was unclear to him how slides 16 and 17 resulted in that statement.

Dr. Petersen replied that knowing how well ACAM2000™ protects against orthopoxviral disease is of interest. Currently, there is little naturally occurring orthopoxviral disease in the world since the eradication of smallpox. Showing efficacy for ACAM2000™ in a natural orthopoxvirus infection would be difficult. These are surrogates for that outcome, which is of primary interest. Cutaneous response has been demonstrated during the smallpox eradication era as a marker of vaccination success. Historically, smallpox vaccines were not studied rigorously. There were no clinical trials to prove efficacy, but their effectiveness ultimately was demonstrated by the eradication of disease. While the WG recognized that these outcomes are surrogates, they felt that this offered significant evidence for protection against orthopoxviral disease.

Dr. Campos-Outcalt emphasized that that differed from the first bullet on Slide 26, which states that ACAM2000™ is comparable to Dryvax®. He did not think that Slides 16 and 17 showed this to be true. In each instance, there is inferiority to Dryvax® in one of the two groups. He was fine with saying ACAM2000™ is believed to be effective, but did not think it was accurate to state that it is comparable to Dryvax.

Dr. Petersen acknowledged that "comparable" is a subjective assessment. Differences were demonstrated in these data comparing ACAM2000™ to Dryvax. The arguments to downplay the differences would be that in terms of the differences between vaccine-naïve and previously vaccinated subjects for ACAM2000™, it is known that the cutaneous response can be affected by previous vaccination. The differences in previously vaccinated subjects may be related to that fact, although the numbers are certainly different. With respect to the neutralizing antibody response, ACAM2000™ did not meet inferiority to Dryvax®, but a robust neutralizing antibody response was observed. The level of antibody response required to provide protection is unknown, and it was very close to meeting non-inferiority.

Dr. Campos-Outcalt stressed that Dryvax® is no longer an issue in that a choice is not being made between ACAM2000™ and Dryvax®. Based on what was shown, ACAM2000™ is not comparable or equivalent to Dryvax®.

Dr. Petersen agreed and acknowledged that reasonable people could have differences of opinion in terms of language and subjective evaluations.

Dr. Karron wondered about the laboratory exposure incidents and the fact that only seven individuals would have met criteria for vaccination, and whether that was because the other 19 individuals were working in laboratories or facilities but not working directly with the virus. That is, who were those other 19 and why did they not meet criteria?

Dr. Petersen clarified that the other individuals were not vaccinated at all. Seven met ACIP vaccination recommendations, and only one of those actually became ill with the disease. The others were exposed, but they were vaccinated according to ACIP recommendations and they did not develop orthopoxvirus infection.

Dr. Schuchat asked whether he meant by "met ACIP vaccination recommendations" that they had received the recommended vaccine, and whether all of these people were in a group that *would have* been recommended to receive vaccine.

Dr. Petersen replied that Dr. Schuchat was correct.

Dr. Weber (SHEA) said that being at the University of North Carolina where there is a large defense group, he has personally taken care of at least two cases from DoD, one with post-vaccinia encephalitis and a contact with generalized vaccinia. He has also cared for several soldiers who had had recent inoculations, still had dressings, and were in his hospital for other reasons. He requested that the word "worker" be changed to "personnel" since he assumed graduate students would be working on this as well, and they are not necessarily workers. This would make the recommendation more inclusive of students and trainees. He found the recommendation for HCP to be much too ambiguous in that it does not provide the precision needed. Also, it does not describe who makes the decision to immunize. Is it the facility? It is important to keep in mind that vaccine must be acquired from the health department. Is it going to be used pre-exposure, such that his hospital should have a group of people who have been immunized? Is it going to be used at the time of taking care of a person with a complication of

vaccinia? Is it going to be used post-exposure? It doesn't say anything about boosters. Are those people immunized just once, or should they be current within 10 years with a booster? He encouraged ACIP to make the recommendation much more precise to give the hospital epidemiologist some guidance as to when vaccinia immunization of HCP is indicated.

Dr. Petersen responded that the WG could attempt to make the language more precise. Revaccination is included, but has not changed from previous recommendations so he did not make it a point to discuss that. Regarding how the vaccine would be used, this is a very specific document targeting a very specific population—persons occupationally exposed to orthopoxviruses. It does not involve persons who may be vaccinated for other reasons. Certainly, DoD makes their own decisions about smallpox vaccination. The recommendation also does not address the potential first responder population. The WG tried to make the recommendation as focused as possible specifically on the laboratory personnel population.

Dr. Weber (SHEA) asked for clarification regarding exactly what HCP the WG was talking about in the recommendation—people conducting research or people at a healthcare facility providing care to people who have developed complications from vaccinia?

Dr. Petersen clarified that the recommendation addresses both of those populations. The laboratory personnel under these proposed recommendations would be recommended to receive smallpox vaccination. The HCW are as described in the proposed language, "health-care workers (e.g., physicians and nurses) whose contact with replication-competent vaccinia viruses is limited to contaminated materials (e.g., dressings) and persons administering ACAM2000™ smallpox vaccine who adhere to appropriate infection prevention measures can be offered vaccination with ACAM2000™." This is more lenient by stating that "vaccination can be offered." For that reason, it is a Category B recommendation.

Dr. Weber (SHEA) emphasized that his only argument was that the recommendation did not provide enough precision to a hospital epidemiologist to know to whom they should offer vaccine, under what circumstances it should be offered, and who is responsible for making those decisions (hospital or local, county, state health departments).

Dr. Decker (Sanofi Pasteur) indicated that since the time of original licensure of ACAM2000™, a family of post-marketing safety studies has been underway. Some of these studies are completed, and others continue. The data that can be provided from those studies at this point, prior to the final analyses, was provided to CDC last year and were not materially changed. In total, nearly a million DoD personnel have been vaccinated and have been under surveillance in one or more of these studies. The information available is robust. The safety dataset is not likely to increase further in coming years due to the cessation of deployments to the Middle East and other factors, which means that DoD vaccinations will not occur at the same rate as in the past. DoD vaccinations represent 99.9% of all vaccinations in the US.

Dr. Romero asked what DoD's policy is regarding their physicians and nurses who administer this vaccine or care for individuals who receive the vaccination.

Dr. Sergienko (DoD) replied that providers are vaccinated as well.

Dr. Romero indicated that he was old enough to have received the vaccine as a child, and to have been a vaccinator during the last round of vaccinations. All vaccinators were vaccinated before they began to give the vaccine. Therefore, he wondered why this would be a Category

B rather than A recommendation and thought the recommendation about how to use the vaccine should be stronger.

Dr. Petersen replied that the Category B recommendation specifically for vaccinators was simply because it has not been studied robustly. Though CDC is not aware of any infections that have resulted from exposures during vaccination in vaccinators, without a strong base of data to support that, the WG felt that it should be a Category B recommendation. However, he was not opposed to making it a Category A recommendation.

Dr. Damon indicated that in the 2002 vaccination program, the decision to vaccinate the vaccinators was made because it was assumed that the vaccinators would also be part of the response. In the case of proposed recommendation, the individuals are simply taking care of patients who are in studies or who are being vaccinated.

Dr. Petersen added that the volume of vaccine being administered by this specific vaccinating population is likely to be much lower, given that relatively few laboratory workers are receiving smallpox vaccine. Their cumulative risk of exposure while vaccinating may be lower than in other larger smallpox vaccination programs.

Dr. Bennet requested additional information about the relationship between known cardiac risk factors and myo/pericarditis. Her understanding of myocarditis is that it could happen to anyone.

Dr. Petersen replied that this was one of the more difficult issues the WG dealt with. It is accurate that there are not any known risk factors for attempting to predict who may have an AE of myo/pericarditis. That rationale used to support this recommendation is that if someone has this AE, they would likely have a more severe outcome based on known disease or known cardiac risk factors.

Regarding Dr. Campos-Outcalt's question, Dr. Plotkin (Vaccine Consultant) indicated that the mechanistic correlate of protection for smallpox vaccine is antibody. Antibody can last as long as 70 years and remains protective, or at least partially protective, during that time. The level of antibody that is protective has been estimated to be 1:32. The GMT of the ACAM2000™ is well above that. However, it might be more useful to give a percentage of those who have titers of 1:32 or greater. There are no data on the cellular response, which is important in closing off the vaccinia replication. The ACAM2000™ vaccine apparently did that, which implies that they did develop a cellular response. ACAM2000™ may not have the same level of response, but as long as the level persists, it should be just as effective as Dryvax®.

Dr. Kempe asked Dr. Petersen whether he could comment on the issue of whether the outcomes for vaccinia virus are substantially less severe and whether any of these analyses have been repeated based on those data.

Dr. Petersen responded that previous studies have assessed historical smallpox vaccine, and it has been observed that the take or cutaneous response to vaccination is ameliorated by previous vaccination. He did not believe this had been evaluated with ACAM2000™, but it could be. That would be one example of direct demonstration of ACAM2000™ protecting against orthopoxvirus infection.

Dr. Moore (AIM) asked how civilian laboratory personnel receive vaccines. They cannot call her office to get them. A graduate student contacted her from another state because they were beginning a project in which they were working with the vaccinia virus and could not obtain the vaccine, but she was unable to assist them. She also wondered whether any safeguards were in place to assure that laboratory personnel who have a Category A recommendation have access to the vaccine, and it is not simply a function of a facility that decides on their behalf whether they will be offered the vaccine.

Dr. Petersen indicated that the policy note includes updated information regarding how to request the vaccine, for which CDC is the only source. The vaccine is made freely available, and explicit instructions regarding how to request smallpox vaccine from CDC's Drug Services is included in the Policy Note. There should not be any barriers to receiving smallpox vaccine. He has heard that one of the primary barriers has been finding someone who is willing to administer the vaccine with the thought that the administrator needs to be vaccinated. Part of the thought in recommending that vaccinators for the laboratory worker population be offered vaccine rather than recommended to be vaccinated is to help ameliorate the potential for barriers to vaccinations for this population.

Dr. Temte emphasized that at this point, there remained a number of unresolved questions pertaining to identification of who should receive the vaccine, whether having a laboratory in the community indicates that one of the local hospitals should have vaccinated staff on board, et cetera. He asked the members whether they wished to continue the session, or preferred for the WG to consider the issues further and engage in additional discussions during the October ACIP meeting.

Dr. Harrison asked Dr. Petersen whether he felt he could address the issues raised and present a revised option the next morning.

Dr. Petersen said he would be happy to discuss with Dr. Weber how to clarify some of the language and identify where there may be deficiencies.

Dr. Temte proposed that they return to smallpox the next day, to which the members agreed.

Revised Proposed Smallpox Vaccine Recommendations

Brett W. Petersen, MD, MPH
Medical Officer, Poxvirus and Rabies Branch, CDC
Lieutenant Commander, U.S. Public Health Service

During the second day of the June 2015 ACIP meeting, Dr. Petersen recapped the issues raised the previous day regarding the proposed smallpox recommendation and reviewed the proposed recommendation as revised. The following issues were raised and addressed:

- Change "worker" to "personnel" in policy note in an effort to be more inclusive. The WG agreed that this would be appropriate in order to be more inclusive and will make this change.

- Revise the proposed recommendation for healthcare personnel. The WG agreed and proposed the following language: "Health-care personnel (e.g., physicians and nurses) that currently treat or anticipate treating patients with vaccinia virus infections whose contact with replication-competent vaccinia viruses is limited to contaminated materials (e.g., dressings) and persons administering ACAM2000™ smallpox vaccine who adhere to appropriate infection prevention measures can be offered vaccination with ACAM2000™ (recommendation category: B, evidence type 2)."

- Regarding the responder population who may have already been vaccinated during the 2002 smallpox vaccine program, the WG thought it would be reasonable to include the following statement in the revaccination section: "Public health and health care volunteers who were vaccinated as responders in the US Civilian Smallpox Preparedness and Response Program should refer to the October 2008 CDC Interim Guidance for Revaccination of Eligible Persons who Participated in the US Civilian Smallpox Preparedness and Response Program which can be found at http://emergency.cdc.gov/agent/smallpox/revaxmemo.asp.

- Regarding post-exposure management, the WG did not feel that there were sufficient data to provide a strong recommendation for the possibility of post-exposure vaccination in persons who have been exposed to an orthopoxvirus. However, the proposed the following addition: "Persons with an orthopoxvirus exposure should be evaluated by a healthcare provider and clinical management decisions including post-exposure smallpox vaccination should be made on a case-by-case basis in consultation with public health authorities."

Vote: Smallpox Vaccine Use in Laboratory Personnel

Dr. Riley made a motion to accept the wording, with the revisions as stated, for the use of smallpox vaccination in laboratory personnel. Dr. Romero seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Day 1: Public Comment

No public comments were offered during this session.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat thanked Dr. Cindy Weinbaum for serving as the Interim Executive Secretary for the ACIP, and let the audience know that Dr. Ray Strikas will be joining ACIP as the Interim Executive Secretary following this meeting. The position for the permanent Executive Secretary will be posted soon. Regarding measles, the outbreak that originated in the Disney parks in California is officially over. However, imported cases do continue and public health is conducting considerable follow-up with each case individually. Early data show that there has been a substantial increase in adult measles, mumps, and rubella (MMR) vaccine uptake this year. It is gratifying that public awareness is increasing. More than half of the cases this year have been in adults who do not necessarily know or have their vaccine history. Since the February 2015 meeting, CDC initiated the Sierra Leone Trial to introduce a vaccine against Ebola together with the College of Medicine and Allied Health Sciences in Sierra Leone and other partners. Thus far, approximately 7000 healthcare and frontline workers have been enrolled and over 3300 have been vaccinated. That campaign is continuing in partnership with the Sierra Leoneans.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance reported that as a result of the measles outbreak, the Centers for Medicare and Medicaid Services (CMS) convened a call with all of its State Medicaid Directors in March 2015. CDC assisted with and participated in that call. The purpose of the call was to remind Medicaid Directors about the importance of maintaining a high level of vaccination coverage, and working with providers to ensure that all Medicare recipients also maintain vaccines. CMS is also working closely with CDC to try to improve Medicaid data to ensure that the Medicaid rate of coverage is clear.

Department of Defense (DoD)

Dr. Sergienko reported that the Department of Defense (DoD) continues to work on its new electronic health record (EHR). Based on recent conversations, he hopes that DoD's Immunization Information System (IIS) will be better integrated with the state's IIS and their programs. DoD is involved in post-marketing surveillance of the adenovirus vaccine. The study is complete and the results should be available shortly. Thus, far the data suggest a sharp decline in deaths. In terms of influenza vaccine for 2015-2016, DoD is partnering with the Office of Personnel Management (OPM) to improve vaccine rate uptake among federal employees on military installations by offering more information through the health benefits program and by offering more vaccines on installations. DoD is conducting a Japanese Encephalitis (JE) vaccine awareness campaign to increase vaccine uptake in Western Pacific areas that are at increased risk. Along with CDC and other partners, DoD is involved in the Ebola Vaccine Trials. The US Army Medical Research Institute of Infectious Disease (USAMRIID) was involved in fielding two of those vaccines.

Department of Veteran's Affairs (DVA)

Dr. Temte read the Department of Veteran's Affairs (DVA) update into the record. The Veterans Health Administration (VHA) continues to work on several information technology (IT) immunization projects to improve documentation of immunizations in EMRs. Current efforts are focused on updates that will provide VA clinicians with greater detail about a patient's immunization history, including vaccine administration dose, route, anatomical location, lot number, manufacturer, and which vaccine statement was provided to the patient. VHA released a set of updated national clinical reminders through their clinical decision report tools regarding two pneumococcal vaccines about two months ago, and plans to release new clinical reminders about Tdap, Td, and zoster vaccine later this year. VHA completed its annual seasonal influenza campaign, with 1.8 million doses administered to veterans. In addition, approximately 10,000 to 20,000 doses of influenza vaccine were administered to veterans during the 2014-2015 influenza season through a partnership between VHA and Walgreens.

Food and Drug Administration (FDA)

Dr. Sun reported that since the February 2015 ACIP meeting, the Food and Drug Administration (FDA) approved a new vaccine, QUADRACEL®, which is an acellular pertussis, diphtheria, tetanus, inactivated poliomyelitis vaccine (IPV) made by Sanofi Pasteur. This vaccine is indicated for children 4 through 6 years of age, given as a fifth dose in their routine immunization series or as a fourth or fifth dose of an IPV routine immunization series. On June 30, 2015, FDA will be implementing the new pregnancy lactation rule for prescriber information. That means that all of the previous pregnancy categories will no longer be used. This is a revision of the way that the labels will look for drugs and biologics, including vaccines. The idea behind this is to better describe the benefits and risks when contemplating prescribing drugs or vaccines for use during pregnancy or breastfeeding women. A new category is included regarding reproductive potential for males and females, which will discuss considerations for the effects of drugs or vaccines on reproductive potential. This rule will be phased in for previously licensed products over the next three to five years, but any new applications received on or after June 30, 2015 will have to comply with this labeling requirement. FDA is working closely with CDC on the Ebola study in Sierra Leone, and with NIH on the Ebola vaccine study in Liberia. A vaccine advisory committee was convened in February 2015 to seek advice on potential ways to license an Ebola vaccine.

Health Resources and Services Administration (HRSA)

Dr. Houston reported that the national Vaccine Injury Compensation Program (VICP) had a very busy year processing claims in fiscal year 2014. A record number of non-autism claims were filed. In the last fiscal year, a total of 633 claims were filed with the VICP. Thus far, 496 claims have been filed in the 2015 fiscal year. The record set last fiscal year is anticipated to be surpassed this fiscal year. To date, there have been 390 adjudications of which 313 were compensable and 77 were dismissed. Awards to petitioners have totaled approximately $169 million to date, and attorneys' fees have totaled approximately $14 million. More data about the program can be obtained on the VICP website: www.hrsa.gov/vaccinecompensation/data. The program has been developing regulations to make changes to the Vaccine Injury Table. First, a Notice of Proposed Rule Making to propose several changes to the table has been developed and is being reviewed by HHS. The Final Rule, adding intussusception as an injury for the rotavirus vaccine, was published on June 23, 2015. A Public Readiness and Emergency Preparedness Act (PREP Act) declaration covering certain Ebola vaccines was signed on December 3, 2014 and became effective December 27, 2014. A few therapeutics were also

added to that declaration. People who have received the covered countermeasures are eligible to file a claim with the Countermeasures Injury Compensation Program (CICP). The CICP and the VICP continue to work on outreach efforts to make the public and providers aware of these safety net programs.

Indian Health Services (IHS)

Ms. Groom reported that the Indian Health Service's (IHS) EHR currently has reminders for all of the routine age-based recommendations. PCV13 was recently added for those 65 years of age and older. More clinical decision support is being explored for high-risk conditions. The IHS EHR system currently includes Hepatitis B for diabetics, and IHS is working on decision supports for people with chronic liver disease. In terms of performance measures, IHS has changed its influenza measure. They have been monitoring influenza coverage among adults 65 years of age and older for many years, but felt that it was time to change the performance measures for the agency to align with Healthy People 2020 to monitor influenza vaccine coverage across the IHS population. A developmental measure also is being explored to assess Tdap and influenza among pregnant women that will help to inform the reminder, and work continues on the development of a composite adult immunization measure to assess coverage for all of the age-based adult recommendations. In terms of influenza, the IHS remains frustrated with its fairly stagnant coverage levels. The Chief Medical Officer has requested that a focus be placed on this initiative, so an aggressive influenza plan has been developed and the regions are being asked to develop plans to help IHS achieve the Healthy People 2020 goal.

National Institutes of Health (NIH)

Dr. Gorman began with some words from the National Institutes of Health (NIH) Director, Dr. Collins, about his Precision Medicine Initiative, "Far too many diseases do not have a proven method of prevention or effective treatments. We must gain better insights into the biology of these diseases to make a difference for the millions of Americans who suffer from them. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyles for each person. While significant advances in precision medicine have been made for select cancers, the practice is not currently in use for most diseases. Many efforts are underway to make precision medicine the norm rather than the exception. To accelerate this, President Obama has now unveiled a Precision Medicine Initiative (PMI)—a bold new enterprise to revolutionize medicine and generate the scientific evidence to move the concept of precision medicine into everyday clinical practice."

The National Institute of Allergy and Infectious Diseases (NIAID) and NIH are also involved in the Ebola vaccine trials in Liberia. A large clinical trial to assess the safety and efficacy of two experimental vaccines to prevent Ebola infections is still open to volunteers in Liberia. The trial is being led by a recently formed Liberia-US clinical research partnership, and is sponsored by the NIAID. The study is called the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL). PREVAIL is a Phase 2/3 study that was originally designed to enroll approximately 27,000 healthy men and women 18 years of age and older. At least three vaccine candidates are being tested currently: NIAID-GSK chimpanzee adenovirus 3 (ChAd3-EBO Z)-based vaccine, the NewLink-MERCK Vesicular Stomatitis Virus (VSVdeltaG-ZEBOV)-based vaccine; and the Janssen-Bavarian Nordic AdVac® Eblola MVA-BN®. There are six major therapeutic candidates for Ebola: ZMapp™, an antibody cocktail that bonds and inactivates the Ebola virus; TKM-Ebola, a small interfering ribonucleic acid (RNA); BCX4430, a nucleoside analog

RNA polymerase inhibitor; acyclovir, a small molecule viral polymerase inhibitor with apparent broad antiviral properties; and favipiravir, which is licensed in Japan for pandemic influenza for which post-exposure efficacy has been shown in mice toward Ebola. An adaptive clinical trial has been constructed for evaluation of the therapeutic candidates of Ebola disease. This design was constructed by the Government of Liberia, the University of Nebraska, and Emory University. This trial will compare enhanced standard of care to enhanced standard of care plus a therapeutic candidate. ZMapp™ is the first candidate. Other agents will be tested based on the supportive data availability of the product. The very heartening decrease in the number of new cases of Ebola makes completion of all of these trials much more difficult.

In addition, there is a supplement to *Clinical Infectious Diseases* titled, "Including Pregnant Women in Clinical Trials of Antimicrobials and Vaccines," which includes six articles [Volume 59, suppl 7, December 15, 2014]. Many of the authors are previous or current ACIP members and liaisons. On the NIAID website, there is a slide show that highlights the notable scientific advances made by NIAID laboratories and NIAID-funded researchers at domestic and international institutions during the fiscal year 2014. Some advances have contributed to much needed vaccines and treatment for Ebola, HIV, and influenza. Others have expanded knowledge of rare conditions, such as prion disease and immunodeficiency disorders. All are representative of how public investment in biomedical research can advance science and benefit human health. Finally, NIAID Division of Microbiology and Infectious Diseases (DMID) clinical trials for vaccine candidates that are ongoing include a Hepatitis C vaccine trial, several influenza H7N9 trials, and an ongoing ZOSTAVX® trial for transplant patients. In development is a West Nile vaccine trial for which the Phase 1 study has been awarded to the Duke VTU site, and Investigational New Drug (IND) enabling studies to allow Phase 1 testing of a universal influenza vaccine candidate.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that the National Vaccine Advisory Committee (NVAC) met on June 9-10, 2015 and finalized three reports that should be available on the National Vaccine Program Office (NVPO) website in the near future. One of the reports deals with vaccine confidence, which is defined as "the trust that parents or healthcare providers have in the immunizations recommended by the ACIP, the providers who administer vaccines, and processes that lead to vaccine licensure and the recommended vaccination schedule." The recommendation categories include better measurement, assessment, and tracking of parental attitudes toward vaccines; development of effective communication and strategies to build vaccine confidence; issues of HCP strategies, including development of materials for them to deal with parental concerns; a focus on curriculum for continuing medical education and physicians in training on vaccination issues; and developing of a working group to assess compensation issues for vaccine counseling. Other strategies included tightening of exemption policies and monitoring and support. The second report deals with human papillomavirus (HPV) vaccination, in which the NVAC endorses the President's "Cancer Panel Report," which is a comprehensive set of recommendations to improve HPV vaccine uptake and includes information pertaining to building communication strategies, strengthening immunization systems in adolescent immunization registries, and a review pertaining to whether the HPV vaccine schedule can be simplified to enhance compliance. The third report addresses the role of vaccines in antimicrobial resistance. The NVAC made a strong case to consider vaccines in efforts to combat antimicrobial-resistance bacteria, including having a liaison on the NVAC from the President's National Strategy to Combat Antibiotic-Resistant Bacteria.

National Vaccine Program Office (NVPO)

Dr. Gellin added that what Dr. Orenstein left out was that there is now a standard clause in every set of NVAC recommendations that states that the NVPO will figure out how to do all of this. He reported that the National Adult Immunization Plan (NAIP) is now in final clearance, which includes a focus on health IT and the importance of registries to keep the information flowing. The National Adult and Influenza Immunization Summit (NAIIS) was convened in Atlanta on May 12-15, 2015. The NAIIS is organized by CDC, the Immunization Action Coalition (IAC), and NVPO. One of the themes was the implementation of NVAC standards for adult immunization practices. Another theme was a focus on implementation science to address the fact that people know what they are supposed to be doing, but do not know how to do it. NVPO's Interagency Vaccine Safety Task Force that includes HHS, VA, and DoD has developed a Vaccine Safety Scientific Agenda, which is located on the NVPO website. NVPO will soon release "A Year in Review" for 2014, which is a magazine style highlight of the many things that occurred in terms of vaccines and immunization. CDC's Office of Women's Health (OWM), the Office of Adolescent Health (OAH), and the NVPO have created a WebMD® program scheduled to begin at the end of June with a consumer/parent focus.

Discussion Points

Dr. Fryhofer (AMA) reported that during the June 2015 AMA House of Delegates meeting, the AMA voted in new policy to tighten the limitations on vaccine opt-outs. The House voted to support legislation eliminating non-medical exemptions for federally funded educational programs for children, and to support state medical societies in eliminating non-medical exemptions for childcare and school attendance in state statutes. The AMA Council on Science and Public Health (CSAPH) and its Council on Judicial and Ethic Affairs (CEJA) developed a joint report that laid out the scenarios. It was amazing testimony that demonstrated how the physicians in attendance were adamant about the non-medical exemptions being all that should be opted out of. This was a very different scene from what would have occurred several years ago. This shows the effect of measles and how things have changed. There is a great opportunity for immunizers to move with this momentum, given that the public now better understands the meaning of herd immunity and what can occur when people are not immunized.

Dr. Weber (SHEA) reported that the University of North Carolina Hospitals has had a policy for a number of years to accept only medical contraindications to vaccines. As a condition of employment, all recommended ACIP vaccines are required for HCP. Two complaints were filed with the Equal Employment Opportunity Commission (EEOC), one regarding Tdap and the other MMR. In both cases, the EEOC ruled that if medical contraindications are accepted, religious objections must be accepted as well. Despite the policy, which was approved by the Attorney General of the State of North Caroline, it was overruled by EEOC.

Japanese Encephalitis Vaccine

Joseph A. Bocchini, Jr, MD
ACIP, Workgroup Chair
Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines Work Group
Professor and Chairman, Department of Pediatrics
Louisiana State University Health Sciences Center

Dr. Bocchini thanked Dr. Temte for his leadership and everyone for the opportunity to serve on ACIP the past four years, which has been a wonderful experience for him.

During this session, Dr. Bocchini provided an update from the Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines WG regarding JE vaccine use. The inactivated Vero cell culture-derived JE vaccine (JE-VC; Ixiaro®) is the only JE vaccine available in the US. JE-VC is manufactured by Valneva, formerly Intercell, and is distributed in the US by Novartis. Inactivated mouse brain-derived vaccine (JE-MB; JE-VAX) is no longer available in the US.

In 2009 the FDA licensed JE-VC for use in adults and ACIP approved recommendations for a primary series in adults. In 2010, the *MMWR* Recommendations and Reports from 1993 were updated. In 2011, ACIP approved recommendations for use of a booster dose in adults based on new information and published a Policy Note in the *MMWR.* In 2013, ACIP approved recommendations for use of a primary series in children and published an additional Policy Note in the *MMWR*.

Once the WG completed the YF vaccine objectives, the WG was tasked with updating the recommendations and guidance for use of JE vaccine. The WG's JE vaccine objectives are to:

- ❑ Review newly available safety and immunogenicity data for JE-VC;
- ❑ Review epidemiology and risk of JE in travelers;
- ❑ Review ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler data with potential changes in recommendations to be presented to ACIP; and
- ❑ Update *MMWR* Recommendations and Reports published in 2010 to include all the additional information.

The updated *MMWR* Recommendations and Reports will include the removal of JE-MB vaccine information and recommendations, the addition of booster dose recommendations for adults, and the addition of the primary series recommendations for children. New JE-VC data to review and incorporate include the following:

- ❑ Post-licensure safety data;
- ❑ Use of a single primary dose in people who previously received JE-MB;
- ❑ Increased and decreased intervals between the two primary series doses usually administered 28 days apart;
- ❑ Co-administration with rabies and meningococcal vaccines; and
- ❑ Duration of protection and additional booster dose recommendations.

Regarding additional expected data and events, by the end of 2015, the DoD post-licensure safety study data may become available. The manufacturer has requested a meeting with the FDA to discuss the acceptability of data for an alternate dosing schedule, co-administration, and booster dose indications. The manufacturer might submit proposed label changes in 2016 related to these data.

The ACIP JE and YF WG plans to present revised *MMWR* Recommendations and Reports to ACIP in October 2015 or February 2016. The timeline will depend upon the availability of data. Additional ACIP votes and policy notes may be needed in 2016 and 2017 as new indications are approved by the FDA.

Pneumococcal Vaccines

Introduction

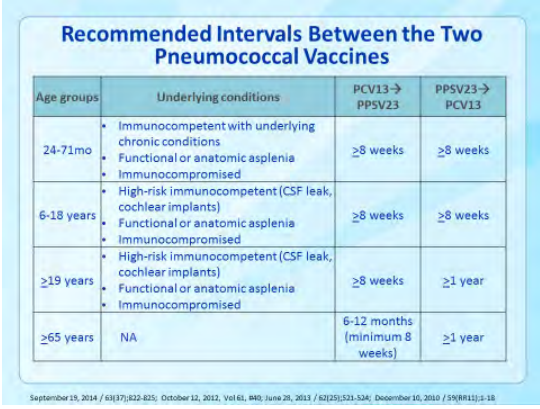
Nancy M. Bennett, MD, MS
Pneumococcal Vaccines Work Group Chair
Advisory Committee on Immunization Practices

Dr. Bennett began by thanking Dr. Temte for his great leadership. The Pneumococcal Vaccines WG has been very busy the last couple of years, and has really appreciated his support.

She reminded everyone that the Pneumococcal Vaccines WG's terms of reference are to:

- Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines;
- Review current recommendations considering up-to-date evidence, including epidemiological studies conducted post-licensure, and assess the strength of the evidence; and
- Revise or update recommendations for pneumococcal vaccine use, as needed.

Both 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) are recommended for adults 65 years or older (ACIP Recommendation, August 2014), and individuals 2 through 64 years of age (ACIP Recommendation, Feb 2010, June 2012, June 2013) who have immunocompromising conditions, functional or anatomic asplenia, or CSF leaks or cochlear implants. The recommended sequence is PCV13 followed by PPSV23. PCV13 is recommended even if an individual previously received PPSV23. The recommended intervals vary by age and risk group, and the vaccine sequence:



Recommended Intervals Between the Two Pneumococcal Vaccines

Age groups	Underlying conditions	PCV13→ PPSV23	PPSV23→ PCV13
24-71mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥8 weeks
6-18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks	≥1 year
≥65 years	NA	6-12 months (minimum 8 weeks)	≥1 year

September 19, 2014 / 63(37);822-825; October 12, 2012, Vol 61, #40; June 28, 2013 / 62(25);521-524; December 10, 2010 / 59(RR11);1-18

The focus of this session was harmonization of the recommended intervals between PCV13 and PPSV23 across age and risk groups. The rational and evidence for the proposed changes to the recommended intervals between PCV13 and PPSV23, and the proposed changes to the recommendations for intervals between PCV13 and PPSV23 were presented for a vote.

Intervals Between PCV13 and PPSV23 Vaccines:
Evidence Supporting Currently Recommended Intervals and Proposed Changes

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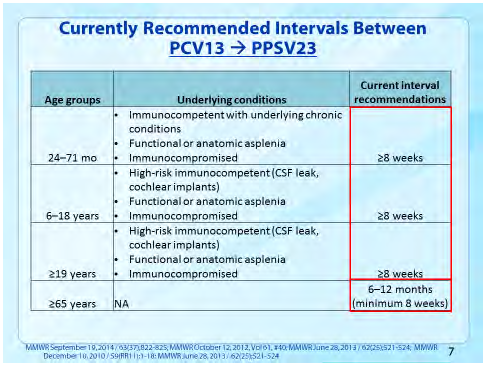
Dr. Kobayashi reminded everyone that currently in the US, two types of pneumococcal vaccines are being used: PCV13 and PPSV23. For individuals with underlying conditions 2 years of age and older and for all adults 65 years and older, administration of both vaccines in series is recommended to maximize protection against pneumococcal disease. When the two vaccines are recommended, PCV13 should be given first followed by PPSV23 whenever possible, as studies have demonstrated that the immune response was greater when PCV was given first. When PPSV23 is given first, there is a recommended interval before administering PCV13. However, under current ACIP recommendations, recommended intervals between PCV13 and PPSV23 are not consistent across age and risk groups, and also depend upon the sequence the two vaccines are given in. As Dr. Bennett outlined and showed in a table, the recommended intervals are different by age groups, risk groups, and the sequence in which the vaccines are given.

Given the complexity of the recommendations, challenges associated with implementing the recommendations, and following many suggestions received by the Pneumococcal WG to harmonize recommendations across different age and risk groups, the WG considered the following question, “Would existing data allow harmonization of intervals between PCV13 followed by PPSV23 and PPSV23 followed by PCV13 across age and risk groups?” In this presentation, Dr. Kobayashi reviewed the sequence of PCV13 followed by PPSV23, which is the preferred and recommended sequence in which the 2 vaccines should be given, and the sequence of PPSV23 followed by PCV13.

Regarding the intervals for the sequence of PCV13 followed by PPSV23, the following table summarizes the intervals that are currently recommended for different groups:



Currently Recommended Intervals Between PCV13 → PPSV23

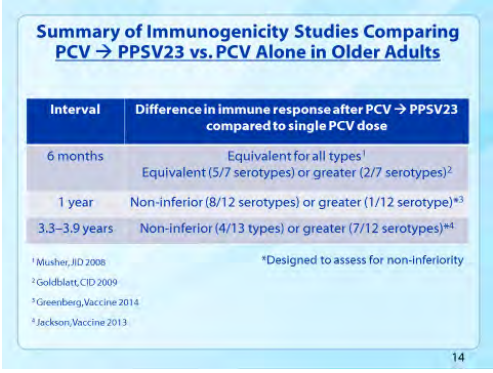
Age groups	Underlying conditions	Current interval recommendations
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥65 years	NA	6–12 months (minimum 8 weeks)

MMWR September 19, 2014 / 63(37);822-825; MMWR October 12, 2012, Vol 61, #40; MMWR June 28, 2013 / 62(25);521-524; MMWR December 10, 2010 / 59(RR11);1-18; MMWR June 28, 2013 / 62(25);521-524 7

There are potentially two ways to harmonize these recommendations, either by changing the interval recommended for children and adults with underlying medical conditions, or by changing the interval recommended for routine administration for adults 65 years and older. Since individuals with underlying conditions listed here are at higher risk of getting invasive pneumococcal disease (IPD), the WG did not think that the recommended interval for these age groups should be prolonged from the current 8 weeks. Therefore, the WG considered changing the interval for adults 65 years and older to be consistent with the younger age groups. However, review of existing literature did not support that change. Thus, harmonizing the interval within the same age group was considered; that is, with the interval recommended for the sequence of PPSV23 followed by PCV13 for adults 65 years and older.

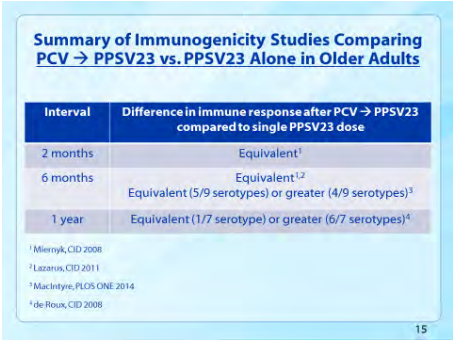
The WG considered several factors when determining whether the change in interval is warranted. The first factor related to implementation and programmatic challenges. As noted earlier, the current interval recommendation for PCV13 followed by PPSV23 for adults 65 years older is different from that of PPSV23 followed by PCV13. Different intervals have caused confusion among healthcare providers administering the vaccine. It also creates challenges in programming vaccine reminders in computer-based programs, as well as use as a quality measure. In addition, Medicare currently covers a different, second pneumococcal vaccine one year after the first vaccine is administered. This suggests that Medicare beneficiaries who received PPSV23 within a year of receipt of PCV13 would not be covered.

The WG then reviewed the existing literature to determine whether the evidence would support changing the interval for the sequence of PCV13 followed by PPSV23 to 1 year or longer in adults 65 years and older. To answer this question, it would be ideal to review clinical efficacy studies designed to directly compare different intervals for the sequence of PCV13 followed by PPSV23. However, only limited data from immunogenicity studies are available and only one study included a direct comparison of intervals. The rest of the studies compared the immune response after the sequence of PCV (either 7-valent or 13-valent) followed by PPSV23, to the response after a single dose of either PCV or PPSV23 using various intervals. The WG compared these results from different studies to assess whether there is an association between the interval in PCV-PPSV23 series and immune response. The following table summarizes results from studies that provided data on comparison between the immune response after the PCV-PPSV23 sequence to the immune response after a single PCV dose:



In this comparison, of interest is whether the immune response after sequential administration would result in responses that are as good as or greater than the response after a single dose of PCV. Of note, the two studies referenced for the 1-year and 3- to 4-year intervals were designed to assess non-inferiority of immune response following the sequence compared to a single dose; whereas, the rest of the studies referenced in this presentation assessed whether the differences between the groups compared were statistically significant. While it is difficult to compare the results across different studies, immune response following the sequence appears to improve with increased intervals between the two doses.

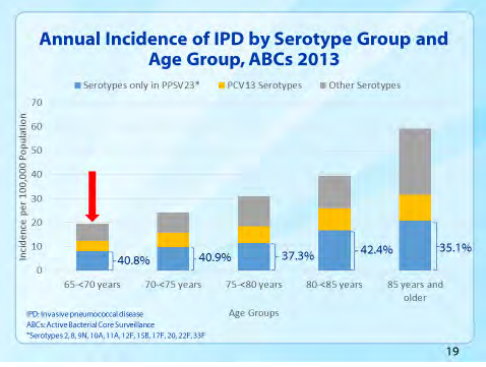
The following table summarizes results from studies that provided data on comparison between the immune response after the sequence of PCV followed by PPSV23, to the immune response after a single PPSV23 dose to assess whether adding PCV before PPSV23 would result in an improved immune response with the interval used in each study:



Here, a tendency also is observed for studies using longer intervals to result in improved immune response, although again, direct comparisons across different studies are difficult to make. One study with direct comparison between different intervals was conducted among Alaska Native (AN) adults ages 55 through 70 years. The results were also included in the previous table. Participants were randomly assigned to three groups, which either: 1) received PPSV23 only, 2) received the sequence of PCV7 followed by PPSV23, 2 months apart, or 3) received the same sequence 6 months apart. Immune response was measured by IgG concentrations and opsonophagocytic assay for 5 pneumococcal polysaccharides. The results showed that the immune responses measured 2 months after the receipt of PPSV23 did not differ among the 3 study groups for any of the 5 pneumococcal serotypes measured. Of note, more injection site swelling that was statistically significant was noted in the group with a 2-month interval compared to the group with a 6 month interval [Miernyk et al. CID 2008].

In summary, none of the reviewed studies were designed to identify the optimal length of the interval between PCV13 and PPSV23. In addition, comparisons across studies are difficult to make given the differences in design or target population. The intervals used in the studies reviewed ranged from 2 months to 3 to 4 years[8]. Comparisons of a response following a PCV-PPSV23 series versus a single dose across studies utilizing these intervals showed that longer intervals, such as a year or longer[6-7], may result in improved immune response compared to shorter intervals such as 2 months[1] or 6 months[1-5]. Of note, the one study that conducted direct comparison between 2 months and 6 months showed that the shorter interval was associated with increased reactogenicity that was statistically significant (p=0.01) [[1]Miernyk, CID 2008; [2]Musher, JID 2008; [3]Goldblatt, CID 2009; [4]Lazarus, CID 2011; [5]MacIntyre, PLOS ONE 2014; [6]Greenberg, Vaccine 2014; [7]de Roux, CID 2008; [8]Jackson, Vaccine 2013].

The following figure summarizes the incidence rate of IPD by serotype and age group from the 2013 Active Bacterial Core surveillance (ABCs) data. These data are observed in a setting of PPSV23 coverage of approximately 60% among adults 65 years or older but before routine use of PCV13 in this age group:

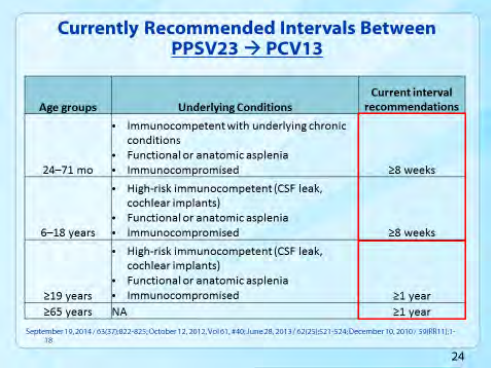


The blue portion of the bar represents the proportion of invasive pneumococcal disease caused by serotypes contained only in PPSV23 and not in PCV13, and is approximately 40% across all age groups. The overall burden of disease, as well as incidence of IPD caused by PPSV23-only serotypes, is higher in older age groups. However, the potential change in the recommended interval will mostly impact those who are younger; that is, those who are turning 65 as they are the ones who are more likely to be naïve to PPSV23 and, therefore, are more likely to receive PCV13 before PPSV23 and be affected by the change in the recommended interval.

In conclusion, the WG considered that changing the interval between PCV13 followed by PPSV23 from the current 6 to 12 months to at least 1 year for adults 65 years and older would be appropriate for several reasons. First, the change will allow for harmonization of the recommendation with the interval for the sequence of PPSV23 followed by PCV13 for the same age group. Second, this will be consistent with the current CMS policy. Third, immunogenicity studies suggest that an interval of a year or longer between PCV13 and PPSV23 is appropriate and may lead to a better immune response compared to the one achieved with shorter intervals. The change in the recommended interval may result in up to 6 months increase in the risk window for invasive pneumococcal disease caused by serotypes only contained in PPSV23. However, 1 year is still within the currently recommended interval, and this change is likely to affect mostly the younger age group, naïve to PPSV23 and whose overall risk of pneumococcal disease is lower within this age group of 65 years and older. Therefore, the WG

proposed to change the interval between PCV13 followed by PPSV23 from the current 6 to 12 months to at least 1 year.

Regarding the intervals for the sequence of PPSV23 followed by PCV13, the following table summarizes the currently recommended intervals for the sequence of PPSV23 followed by PCV13 by different age- and risk- groups:



Currently Recommended Intervals Between PPSV23 → PCV13

Age groups	Underlying Conditions	Current interval recommendations
24–71 mo	• Immunocompetent with underlying chronic conditions • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
6–18 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥8 weeks
≥19 years	• High-risk immunocompetent (CSF leak, cochlear implants) • Functional or anatomic asplenia • Immunocompromised	≥1 year
≥65 years	NA	≥1 year

To harmonize the recommendations, either the recommended interval for children with underlying conditions can be changed from 8 weeks or longer to 1 year or longer, or the recommended interval for adults can be changed from 1 year or longer to 8 weeks or longer. However, the recommendation of a 1 year or longer interval for adults was made based on data from immunogenicity studies suggesting blunting of immune response to PCV13 with shorter intervals between PPSV23 and PCV. Therefore, the WG reviewed the literature to determine whether evidence would allow a change in the recommended interval in children with underlying conditions to harmonize it with the interval recommended for the adult groups.

There were a number of considerations with regard to harmonizing the recommendations. First, the proportion of children who potentially will be affected by this recommendation is small. Groups of children for whom this recommendation may be applicable include: 1) children who were 2 years or older who were indicated to receive PPSV23 before PCV7 became available in 2000 (e.g., the current cohort of 17 to 18 year olds); and 2) children with underlying conditions who, for whatever reasons, did not receive any PCV13 or received incomplete PCV13 series as infants, and have already received a dose of PPSV23. Second, there are programmatic issues and practical aspects. The change will make the recommended interval different from the current interval for PCV13 followed by PPSV23. Conversely, the proposed changes would allow for harmonization of recommended intervals for this sequence across all age groups, and would harmonize intervals for both sequences for those with underlying conditions. In addition, the change is likely to affect only a small number of children, as explained earlier. Therefore, the WG felt that these proposed changes would not likely pose substantial implementation challenges for the majority of providers.

The WG reviewed the existing literature to determine whether the evidence would support the change of the interval for the sequence of PPSV23 followed by PCV13 from 8 weeks or longer to 1 year or longer in children ages 2 through 18 years with underlying conditions. As stated earlier, it would be ideal to review clinical efficacy data that are designed to compare different intervals for the sequence of our interest. Since those were not available, the WG reviewed data from existing immunogenicity studies. Immunogenicity studies from adults have suggested that there may be a blunting of immune response to PCV when given after PPSV23, especially when the interval between the sequence was a year or less. Based on these data presented to

the committee during previous meetings, for adults, a 1 year or longer interval was recommended for PCV receipt post-PPSV23.

In terms of whether the evidence supports the change of the interval for PPSV23 followed by PCV13 to ≥1 year for children 2 through 18 years of age with underlying conditions, limited data from immunogenicity studies are available. There are data suggesting blunting of immune response to PCV when the interval is ≤1 year after PPSV23 in adults[1-7]. An interval of >1 year is recommended for adults. The WG reviewed available studies in children comparing the response after the sequence of PPSV23 followed by PCV7 to the response after a single dose of PCV7, to assess whether PPSV23 receipt before PCV7 administration given the interval used would result in decreased immune response. No studies using PCV13 were available for this comparison. The WG also reviewed one single arm study among children with sickle cell disease who have received PPSV23 prior to study enrollment. No comparison group was available in this study, but the response post PCV13 was evaluated, and the immune response post PCV13 was assessed by time since PPSV23 receipt [[1]Lazarus, CID 2011; [2]Musher, JID 2008; [3]de Roux, CID, 2008; [4]Jackson, Vaccine, 2013; [5]Greenberg,Vaccine 2014; [6]Crum-Cianflone, JID 2010; [7]Miiro, JID 2005].

Among the reviewed studies, there was no clear evidence of blunting of immune response when PPSV23 was given before PCV7 in comparison to the response after a single dose of PCV7. However, none of the studies had intervals that were less than one year. Regarding the results from a single-arm study that assessed children with sickle cell disease with a history of previous PPSV23 at least 6 months before enrollment, the median time since the receipt of PPSV23 was 2.9 years, with a range of 6 months to 11.8 years. The results showed that children were able to mount an immune response after administration of PCV13, and there was no correlation between time since PPSV23 and response to PCV13 [Montalembert, Pediatr Blood Cancer 2015].

In summary, none of the reviewed studies were designed to evaluate the optimal interval between PPSV23 and PCV13 in children with underlying conditions. From the reviewed studies, there was no evidence of blunting of immune response when PPSV23 was given before PCV7 compared to the response after a single dose of PCV7; however, all of these studies had an interval of at least 1 year between the two vaccines. The intervals evaluated were 1 year[1], 18–39 months[2], 5 years[3]. Results from a single-arm study showed that there was no correlation between time since last PPSV23 and response to PCV13, but again, the minimum interval was 6 months [[1]Blum 2000 Vaccine; [2]Spoulou, Vaccine 2005; [3]Mikoluc, Eur J Clin Microbiol Infec Dis 2008; [4]Montalembert, Pediatr Blood Cancer 2015].

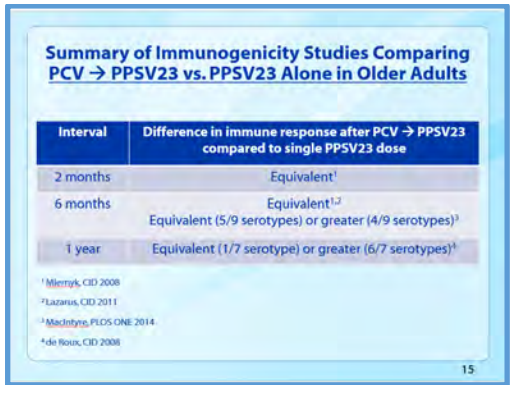
In conclusion, the WG considered that changing the interval for the sequence of PPSV23 followed by PCV13 from at least 8 weeks to 1 year for children 2 to 18 years with underlying conditions would be appropriate for several reasons. First, this would allow harmonization of the recommended intervals across all age groups with underlying conditions. Second, the proportion of children affected by this change would be small and this would only apply to those who already received a dose of PPSV23 and are eligible to receive PCV13. Third, this interval would avoid potential blunting of immune response to PCV13. Although the blunting was not evident from the reviewed studies, none of the studies had an interval shorter than 6 months. This change, however, will make the recommended interval different from the recommended interval for the sequence of PCV13 followed by PPSV23 for the same group.

Discussion Points

Given that there have been PCV13 recommendations for 10 months, Dr. Temte wondered whether there was information about how many people over the age of 65 have received PCV13 followed by PPSV23 6 months later. To his knowledge, this was not occurring in practice in order to avoid the financial burden this would place on seniors. Dr. Kobayashi replied that they did not have this information in hand.

Amy Groom (IHS) indicated that IHS does not have coverage data yet, but has programmed a reminder to give the PPSV23 at 6 months, because they felt urgently that the burden of disease in the IHS population was high enough that they wanted to administer that dose as quickly as possible. She remains concerned that there seemed to be a CMS policy issue that may be driving a change to 12 months rather than 6 months.

Dr. Harrison shared Ms. Groom's concern, expressing his curiosity about why CMS would not permit payment in accordance with ACIP guidelines. He also noted that the term "may be better" was being used. He requested a review of the data showing that it is better, because the data did not seem overly overwhelming. He wondered if what led to the statement was the 6 of 7 versus 4 of 9 when the immunogenicity studies were reviewed. He also requested information regarding the GMTs.



Dr. Kobayashi replied that there are no clinical data comparing the intervals directly. The recommendations are based on the immunogenicity studies. These studies used certain intervals, and were compared using different intervals. For example (referring to the slide Dr. Harrison questioned), the data presented were derived from a summary of studies using the sequence of PCV followed by PPSV23 using different intervals, compared to the immune response after a single dose of PPSV23. The 2-month interval and the 6-month interval were done in the same study. The investigators compared the immune response following PPSV23 at 2 months between the intervals in one group, and at 6 months between intervals in another. That study did not show any statistically significant difference between the two groups in the responses. The result of the study that used a 1-year interval between PCV followed by PPSV23 showed that 1 out of the 7 serotypes measured had a greater result compared following the sequential dose versus the response after a single PPSV23 dose and 6 out of 7 had a greater response after the sequential administration compared to a single PPSV23 administration. Dr. Kobayashi indicated that she had not included the slide showing GMTs.

Dr. Schuchat noted that the vast majority of pneumococcal vaccines in adults are given in the fall. The incidence of pneumococcal disease in seniors is not flat during the year, so the incidence or risk of disease in a 6-month period could be quite different depending when the 6th month is. Therefore, she did not think the urgency about missing 6 months of coverage was necessarily a major issue. GMTs are not necessarily correlated with protection, so there is a lot of grayness regarding how to interpret the GMTs.

Dr. Moore (SME) added that provider confusion seems to be driving the CMS issue. The number one question CDC has received since this recommendation is, "What is going on with these intervals? Why is it one way for this group and another way for that group?" He received an email the previous day from a provider who is in charge of programming their electronic medical records and decision support for pneumococcal vaccines, who asked whether ACIP was going to take up this issue. The CMS issue is not driving this. It is all about making it easier for providers to adhere to the recommendations.

Dr. Temte reinforced Dr. Schuchat's comment and invited those interested to go on the influenza website to look at the pneumonia and influenza death index. The seasonality of pneumonia deaths in this country is remarkable, and is largely confined to about a 4-month period every winter.

Dr. Schuchat emphasized that there is an enormous amount of public and private health promotion every fall to promote influenza and pneumococcal vaccines. It would be much easier to take advantage of that in terms of trying to implement recommendations for a first or follow-up vaccination. It is also a good time to protect people before the intense season of pneumonia and influenza. The 6-month interval is not as practical from that point of view as a 1-year interval.

Dr. Lett (CSTE) indicated that as one of the people who provides clinical decision support for their registry, they are changing these intervals. For them, it is black and white in terms of marking doses valid or not valid. Their registry is programmed not to recommend another dose if the interval is too short based on consultation with CDC. She asked for clarity about repeating a dose in those for whom the interval is too short between doses.

Dr. Campos-Outcalt asked how many serotypes were measured and why, and if the studies Dr. Kobayashi presented were measuring the 23 in PPSV, the 13 in PCV, or the 7 in PCV.

Dr. Kobayashi responded that the MacIntyre study measured the serotypes that were common. The results shown included a mixture of those studies for PCV7 and PCV13, which was the reason the PCV type was not specified. The serotypes they measured are usually the common serotypes between PCV and PPSV23. Sometimes, they only chose a few serotypes that were common based on various reasons, so the denominator is basically all of the number of serotypes that they measured that were common between the two.

Dr. Campos-Outcalt said he was having a hard time reconciling the decision not to change the interval for the high risk groups, and he wondered what the rational was behind not making the intervals shorter for the older adults or longer for the high risk adults.

Dr. Kobayashi clarified that these data were only from studies that were conducted in older adults. The studies in higher risk populations were conducted using short intervals. Basically, there is no good evidence to support making the intervals longer. The problem is basically the lack of good data to support an optimal interval.

Dr. Bennett noted that another consideration is that the majority of the over 65 group is relatively healthy; whereas, the people for whom this vaccine is being recommended in the younger groups are at high risk.

Speaking as a pediatrician, Dr. Baker (IDSA) indicated that there are data for the 8-week interval in children at high risk. Speaking for the IDSA, there was robust interest among those in public health. The Chair of IDSA's Public Health Committee is Dr. Geoffrey Duchin. One of the WG members is also a member of the Public Health Committee. If there were sufficient data, she believes they would show that an 8-week interval is too soon. From a practical point of view, people in the age group go to the doctor once a year if they are healthy. They go when CMS is going to pay for it. One of her colleagues went in at 6 months, found out she was healthy, and chose to return later when she learned that she would have to pay out of pocket. The IDSA's position is that this is not perfect, but they are very supportive of the proposed recommendation. She asked whether there would be more data forthcoming.

Dr. Kobayashi said that unfortunately, she did not have the answer to whether there will be additional data in the future that would offer a better basis for the recommendation.

Dr. Schuchat added that the program is planning to conduct a post-licensure vaccine effectiveness study in adults. As mentioned before, the antibody levels are very difficult to interpret. The reality is that a lot of vaccination is being administered in a variety of intervals and sequences. However, more data will be forthcoming in the next few years.

Dr. Whitley-Williams (AMA) noted that while coverage rates are 60% overall, coverage rates in Black Americans and Hispanics are approximately 45% to 46%. Although it does not directly address the issue of the intervals, if people 65 or older do not obtain their first vaccine, it is unclear how much difference this recommendation will make to the burden of disease, particularly in high risk populations. Also, under-represented minority populations tend to have higher complications in terms of diabetes, cardiovascular disease, asthma, et cetera. They certainly would fall into the high risk groups as well. This is obviously not an easy problem to solve. She emphasized the importance of recognizing the disparity.

Dr. Paradiso (Pfizer Vaccines) explained that regarding a dose of conjugate vaccine, adults over 65 make a nice response and then it wanes quite rapidly; however, it is efficacious for 3 to 4 years after that and probably beyond. A polysaccharide dose afterward is not required for that efficacy. The dose will renew that response post-conjugate vaccine, but it is not required for efficacy. The only reason for the polysaccharide vaccine is for the other 10 serotypes, not for the efficacy of the original 13. The discussion regarding the interval that achieves a higher booster after an initial conjugate vaccine is not really that important, because that booster is not needed for efficacy against the 13 types. The interval should be about programmatic issues and about what works best for getting people vaccinated, rather than efficacy against the 13 types.

Dr. Schmader (AGS) indicated for the record that the AGS strongly supported the 1-year harmonization. There has been a lot of confusion amongst patients and providers of older adults, and this will reduce the confusion.

Dr. Temte expressed great appreciation for the IDSA and AGS comments, because they conveyed the type of information needed in terms of practicality.

To further Dr. Harrison's point, Dr. Grabenstein (Merck Vaccines) indicated that the equivalents are at Day 30 and the differences dissipate. Merck has a study underway to assess several dosing intervals between PCV13 and PPS23, which are anticipated to be available in 2016. Regarding Dr. Schuchat's point, pneumococcal vaccine delivery spikes in the fall, coinciding with influenza, but vaccine delivery occurs all 12 months. Vaccination of adults should be available when it is convenient to them, even if that is in February, March, April, May, June, and July. That is hindered by reimbursement constraints, and it is enabled by education. When the patient presents, the clinician should evaluate and vaccinate them regardless of the clock. He agreed that the ethnic disparities are substantial and unacceptable.

Dr. Reingold emphasized that part of the problem pertains to reimbursement by CMS, and he wondered whether there was a way to change CMS policy.

Ms. Hance (CMS) responded that at this point, CMS does not feel that there are enough data. The decision was made based on the information currently available. As they heard throughout the session, there are no data supporting the intervals. The original decision was made by CMS based on a number of factors. First, the two inconsistent intervals must be defined. Medicare does not track which pneumococcal vaccine is given first. Given the two intervals, the common point was 12 months. In addition, as Dr. Schuchat mentioned, there is a very robust combined pneumococcal and influenza vaccine campaign that occurs once a year. It seemed logical to maintain that 12-month period and to continue to include the pneumococcal emphasis during the influenza and pneumococcal campaign. If there are additional studies, CMS is certainly happy to review them and to follow up with CDC and the ACIP. At this point, without further information regarding the intervals, CMS feels they have made the best decision possible at this time.

Dr. Schuchat publically thanked CMS for the extremely speedy regulation they created regarding the conjugate vaccine. She reminded everyone that any type of change would likely be slow.

Dr. Vazquez noted that while the proposed changes would harmonize the pediatric ages with the adult ages, it would do the opposite in terms of children only. In some ways, she thought this made it harder and more confusing for pediatric providers.

Dr. Kobayashi replied that the WG did discuss this to some extent, but were also thinking about the fact that the recommendation addresses children with underlying conditions. These children will likely be seeing specialists who may have populations that cross the 18-year old age group. That issue, harmonization, and immunogenicity were all considered in terms of developing the proposed recommendation.

Dr. Schuchat reminded everyone that the conjugate vaccine for children has been used for 15 years and there is extremely high coverage. The actual number of children who will have received a polysaccharide vaccine prior to conjugate vaccine may not even be in the double digits; whereas, the vast majority of the pediatric issue pertain to very high risk children who should receive polysaccharide after conjugate vaccine. This is less about practitioner confusion than the desire for a shorter interval because these children are at very high risk. Of people 65 years of age and older, 70% have already received the polysaccharide vaccine. Each year, a lot of people are aging into the 65 year old cohort who will be starting with the conjugate vaccine.

Dr. Temte pointed out that in primary care, the vast majority of children to whom this applies have sickle cell anemia. Children with other high risk conditions are being seen by pediatric infectious disease clinics, et cetera.

Dr. Byington (AAP) indicated that the AAP has similar concerns as Dr. Vazquez about the confusion for pediatric providers. AAP would like to see real numbers. The 17 through 18 year old cohort is very small and will age out. However, they still exist and they are at the highest risk, often coming from populations with disparities like sickle cell disease and HIV. AAP is willing to delay the administration of the more effective vaccine from 8 weeks to a year for children who also require 2 vaccinations by AAP guidance. That is, they need to receive 2 vaccines after the PPSV23. The delay is the concern for AAP.

Regarding complexity and using clinical decision support with the immunization registry, Dr. Belongia indicated that the Marshfield Clinic has clinical decision support built into its registry, so this is all programmed into the rules. From a programming standpoint, this could result in a substantial amount of work. Which vaccine was given first is important in terms of programming this vaccine for children.

Dr. Moore (AIM) indicated that AIM programmatically appreciates the simplicity. She was recently asked by their nurses to assess their own protocols because there was so much confusion in health departments. For programming purposes, it will be helpful to highlight in the catch-up schedule what the true minimum intervals are so that there are not flags for repeat vaccines that were given according to acceptable minimum intervals. That is, doses should not be considered invalid that were administered by the previous guidance.

Dr. Loehr (AAFP) thought that from a practical point of view when assessing a patient, practitioners would be looking horizontally rather than vertically in terms of who is at high risk, rather than when they received PPSV23.

Melvin Kahn (MERCK) indicated that the comments alluded to from providers reflected the type of feedback they have been hearing from the marketplace. Given the difficulties in ensuring a second dose of vaccine, covering 40% of IPD is not a trivial issue.

Dr. Baker (IDSA) said, speaking for the IDSA and with respect to the AAP, IDSA is very interested in the topic and is fully supportive of the proposed changes, realizing that there are the issues mentioned.

Regarding horizontal harmonization versus vertical, Dr. Pilishvili clarified that for adults 19 years of age and older with immunocompromising conditions, the WG members agreed that the data warranted a 1-year interval because immunogenicity studies show that there may be some evidence of a blunting of the immune response when PCV is even close to PPSV. In terms of children and this change, there are no data with an 8-week interval. Therefore, they could not assess whether the same concern existed in terms of potential blunting in pediatric studies because none of the studies reviewed utilized the 8-week interval. The interval was a year or longer.

Proposed Recommendations

Tamara Pilishvili, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases

For each group for which the WG proposed a change, Dr. Pilishvili highlighted the current recommendation language and presented the proposed change.

The current recommendation for the intervals between PCV13 followed by PPSV23 among adults ≥65 years of age is as follows:

> The dose of PPSV23 should be given 6 to 12 months after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.

For adults ≥65 years of age with no previous pneumococcal vaccine (PCV13 or PPSV23), the WG proposed the following guidance on intervals for sequential use of PCV13 followed by PPSV23:

> A dose of PPSV23 should be given at least 1year following a dose of PCV13. The two vaccines should not be co-administered. If a dose of PPSV23 is given earlier than the recommended interval, the dose need not be repeated.

The current recommendations for the intervals between PPSV23 followed by PCV13 among children 2 through 18 years with underlying conditions is as follows:

Infants and Young Children <6 Years

- History of complete PCV7 vaccination
  - For children who have underlying medical conditions, a single supplemental PCV13 dose is recommended through 71 months. This includes children who have received PPSV23 previously. PCV13 should be administered **at least 8 weeks** after the most recent dose of PCV7 or PPSV23 [*MMWR* December 10, 2010].

Children 6 Through 18 Years

- Children aged 6 through 18 years who have not received PCV13 and are at increased risk for IPD because of anatomic or functional asplenia, including SCD, HIV infection, CSF leaks, cochlear implants, or other immunocompromising conditions; and who previously received ≥1 doses of PPSV23 should be given a single PCV13 dose **≥8 weeks** after the last PPSV23 dose, even if they have received PCV7 [*MMWR* June 28, 2013].

For children 2 through 18 years of age with underlying conditions, the WG proposed the proposed the following guidance on intervals for sequential use of PPSV23 followed by PCV13:

> A dose of PCV13 should be given at least 1 year following a dose of PPSV23. The two vaccines should not be co-administered. If a dose of PCV13 is given earlier than the recommended interval, the dose need not be repeated.

Discussion Points

Dr. Hahn (CSTE) thought the second sentence seemed confusing. It was not clear to her why there was another sentence saying the vaccine should not be co-administered, because the first sentence states that it should be given a year later and should rule out that possibility.

Dr. Pilishvili clarified that this sentence was already in the recommendation. It was in response to multiple questions received and multiple scenarios in which a provider states that two vaccines were given together. It was not obviously clear even based on previous pediatric recommendations. Because these scenarios have arisen, the WG thought there should be clarification that these vaccines should not be co-administered.

In terms of the pediatric proposed longer interval if PCV13 is being given after PPSV23, Dr. Rubin thought that historically there was an 8-week interval. However, that was before there was an appreciation for blunting. Even though the data are limited, there is no blunting with a 1-year or longer interval. He thinks that is considerable, because the typical patient would be a sickle cell patient who is 3 or 4 years of age who perhaps has received the 23-valent vaccine. The concern is about protecting them over the next 5 to 10 years versus the next 10 months, which would be the interval. That is a reasonable concept based on the data and older individuals.

Dr. Fryhofer (ACP) thought that, as a practitioner, the statement about not co-administering is such an important issue for the immunogenicity, it should remain.

Ms. Pellegrini said she was having trouble with this as a layperson, because to her the first and last sentence said, “You should wait at least a year to give this vaccine, but really, do it anytime you want because there’s no minimum and we say you don’t have to repeat the dose. So, it doesn’t matter if you wait a year or not, or any amount of time, as long as they aren’t actually co-administered.”

Dr. Pilishvili said the chain of thought as the WG was developing this recommendation language was that the main sentence would state the preferred interval, while the following sentences clarified what should/should not happen. What should not happen is that the vaccines should not be given together. The last sentence is essentially to allow for flexibility, because the evidence is weak. Whatever the evidence, the preferred statement is in the main sentence.

Dr. Schuchat said that as an internist, it was surprising to her to learn about the incredible adherence and programmatic aspects of pediatric vaccination. In response to the layperson question, because she was a layperson 10 years ago, she would say that there are a number of pediatric vaccines that do not work if given too young, or at too short of an interval. In the pediatric practice and the immunization registries, the programmatic people who work on that are very focused on valid doses and invalid doses and making sure that children are complete and up-to-date on valid doses. The second red sentence really speaks to whether a dose

counts and if another one needs to be given, as opposed to the science that 8 weeks is probably going to work. Many people have had the 8-week interval. Going forward, the WG would like to give the direction to program in a 1-year interval. People are focused on what constitutes a valid/invalid dose because they are going to keep vaccinating until a patient has all of the valid doses recommended.

Dr. Kempe thought the issues regarding harmonization of the adult and pediatric recommendations were entirely separate, and she wondered if they should separate them because it harmonizes on the adult side, but not the pediatric side. She thought Dr. Rubin's comments were compelling, and said she would like to hear more from the Pediatric Infectious Diseases Society (PIDS) and the Infectious Disease Society of America (IDSA) about how strong a case there is.

Dr. Vazquez said she would also like to hear more about this if, indeed, it was based on blunting. As a practitioner, if she read the second red line in the statement and her patient received PCV13 two weeks after PPSV23, then that dose would count. If the second red statement remained, it should state "if the interval between those two was at least 8 weeks."

Dr. Pilishvili said that would be like stating an 8-week minimum interval, which is what the recommendation was before. But, the way the 8-week interval was interpreted before was that if it was 7 weeks and 1 day, the dose would be invalidated and given again. There is no way of giving guidance on how/when to do that.

Dr. Vazquez said somebody who had two doses that were not co-administered but were given within 2, 3, 4 weeks of each other, according to this, that would count.

Dr. Pilishvili agreed. On a case-by-case basis, this is the recommendation CDC has been giving. There is no guidance to give on how to repeat doses; therefore, the instruction is "do not repeat." Regarding what Dr. Schuchat was saying, there was discussion with the General Recommendations WG and the Immunization Services Division. All of the language that is in the pediatric recommendations about the minimum intervals applies to the same product. In other words, it is the minimum interval between the PCV doses and validation of that, because there are data that this results in the optimal immune response. There is a different issue here with 2 different vaccine products.

Dr. Vazquez asked whether they had to vote on both of the proposed changes, or if the recommendations could be split.

Dr. Temte replied that as an ACIP member, Dr. Vazquez could make a motion to split them. He said that being primarily an adult provider currently, the practicality of the adult recommendation trumped all of the science. His goal is to get his patients vaccinated. If he can do that in a simple way that is paid for, everyone is happy. On the other hand, he was hearing a lot of discussion, especially from their pediatric colleagues, that more information would be nice. He thought it would be reasonable to spit the two recommendations, and perhaps move forward with the adult vote during this session and have the WG bring back the pediatric recommendation during the October 2015 ACIP meeting.

Dr. Bennett pointed out that the only objection the WG would have about bringing back the pediatric recommendation in October is that there will not be any additional data to present at that time.

Dr. Gemmill (NACI) suggested that for clarity, perhaps the word “inadvertently” could be added to the second red line to be very clear that this is not what is recommended as a practice, but if it occurs, the dose does not have to be repeated.

Dr. Sawyer (PIDS) reminded everyone that this sequence of vaccines for children would apply to a very small number of now mostly late adolescents; therefore, he did not think they should spend too much time on this. Coupled with the adult data which show blunting and the lack of data in children, there is no biologic reasons to think children might not also have blunting. He thought they should accept the recommendation as presented.

Dr. Kimberlin (AAP) noted that there have been no reports in the literature to show that the current recommendation of ≥ 8 weeks of separation has resulted in failures. While there are no data to suggest that the 8 weeks is correct, there are also no data to suggest that there is blunting. The adult data are also limited, and there is no clinical correlate that suggests that there is a problem currently. The proposed change pertained to very small numbers of children who will soon age out if the rest of the schedule is being applied correctly. This means that they would be voting on a change that would introduce disharmony for the pediatric recommendation in what appeared to be an effort to harmonize across the columns rather than down. He thought that would impact major numbers of people. Though there may not be additional data, it may be beneficial for the pediatricians to consider and discuss this further internally and return later with a unified voice rather than the current disunity.

Dr. Bocchini agreed that the pneumococcal recommendation was becoming increasingly more complicated over time. However, he thought they had been working to educate pediatricians to provide the vaccines based on the recommendations that exist currently. This is a time-limited phenomenon because these patients are going to age out. The new *Red Book* that was just published has the current recommendations. He thought they could work through this without changing the recommendations and without trying to change what pediatricians do currently, and that no one would be harmed.

Dr. Zucker (NYC Immunization Program) offered some programmatic and practical considerations. As someone who writes standing orders for pharmacists and nurses, she has had tremendous problems trying to explain the pneumococcal recommendations. The easiest and clearest message for her to give practitioners in New York City is to say, “For children, the interval between pneumococcal vaccines is 8 weeks and for adults it is 1 year.” It also is simpler for their registries. If ACIP kept the pediatric recommendation as is, she would not have to reprogram her registry. They have not yet programmed all of the adult pneumococcal recommendations because they have had so much difficulty doing the programming. Based on the conversation, she will take out any minimal interval, and will accept any dose given after the other dose as that is the simplest approach. The sentence regarding co-administration is confusing and requires, because CDC also says that “if you do co-administer, you don’t need to repeat the dose.” When is “given earlier?” Is it 1 day after the previous dose? In fact, if it is 5 minutes after 1 dose, it is still accepted.

Dr. Baker (IDSA) agreed that there was a problem with the second and third sentences.

Dr. Middleman (SAHM) pointed out that some older teens have issues in terms of being eligible for VFC. If there is a 1-year interval, it may mean that some teens can receive the first dose, but will not be covered a year later by the VFC.

Dr. Temte asked the ACIP members whether they wished to vote on both the adult and pediatric recommendations together, or separate out the adult recommendation and have the WG communicate further with ACIP's pediatric colleagues to seek unanimity and return with the pediatric recommendation in October.

Dr. Schuchat said that listening to the conversation, it seemed like the preferred motion was about the adult recommendation only. She pointed out that the pediatric issue pertained to more to catch-up rather than a routine recommendation, and ACIP could decide not to vote on it and have the WG bring it back at a later time. However, that did not mean they were obligated to bring it back for a future vote if they chose not to do so. The driving feature for the WG was a new vaccine for adults, and that being incredibly confusing.

Dr. Temte said they could leave it to the wisdom of the Pneumococcal WG. He said that one of his favorite movies is the "Princess Bride" and the advice there is "Never get involved in a land war in Asia." His advice to Dr. Bennett was always schedule more time for any pneumococcal discussions, because this is always the case.

Vote: Pneumococcal Vaccines

Dr. Belongia made a motion to adopt the adult language and leave standing the pediatric language. Dr. Vazquez seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Belongia, Bocchini, Campos-Outcalt, Harriman, Harrison, Karron, Kempe, Pellegrini, Romero, Reingold, Riley, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Combination Vaccines

Formation of Combination Vaccines Work Group

Arthur Reingold, MD
University of California, Berkeley
Chair, ACIP Combination Vaccines Work Group

Dr. Reingold offered his gratitude to Dr. Temte for his chairmanship over the last few years. He reminded everyone that the ACIP has a number of WGs, some of which are permanent due to need and others of which are temporary. The Combination Vaccine WG is a new WG. Its existence should be relatively brief and is likely to conclude following the October 2015 ACIP meeting.

The benefit of combination vaccines is the ability to combine equivalent component vaccines into single products to prevent more than one disease or to protect against multiple strains of infectious agents causing the same disease, reduce the number of injections, reduce concern regarding number of injections, and improve coverage and timeliness.

The ACIP Combination Vaccines WG was formed in February 2015 to review published and unpublished data related to the safety and immunogenicity of 2 new combination vaccines: 1) Quadracel® DTaP-IPV vaccine for children 4 through 6 years of age; and 2) an investigational hexavalent pediatric vaccine (DTaP5-IPV-Hib-HepB), which is a 3-dose series for children at 2, 4, and 6 months of age.

Quadracel® is a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine. It is intended as a second DTaP-IPV vaccine that is licensed for use in children 4 through 6 years of age. It is indicated for use as fifth dose in a DTaP series and fourth or fifth dose in an IPV series in children who have received 4 doses of Pentacel® or Daptacel®. The Biologics License Application (BLA) was submitted to FDA on March 24, 2014. The BLA was accepted by FDA for review on May 22, 2014. The FDA approved licensure on March 24, 2015.

A multicenter, randomized, controlled, Phase 3 clinical trial has been conducted comparing DTaP-IPV (Quadracel®) to separately administered DTaP (Daptacel®) and IPV (IPOL®) vaccines in children 4 through 6 years who were primed with 4 doses of Daptacel® or Pentacel®. The Combination Vaccine WG will review the Quadracel® data and will be presenting information to the ACIP during the October 2015 meeting.

The investigational pediatric hexavalent vaccine includes antigens for diphtheria, tetanus, pertussis and polio and is a combined product of vaccines made by Sanofi Pasteur and Merck. It is intended as a 3-dose series (2, 4, 6 months). The BLA was accepted by FDA for review in October 2014, and licensure is anticipated in Fall 2015. Over the course of the summer, Sanofi Pasteur and Merck will present information to the WG by teleconference. The WG will review the safety and immunogenicity data, and the plan is to present the hexavalent pediatric vaccine to ACIP for an ACIP and VFC vote during the October 2015 meeting. A draft *MMWR Notice to Readers* is anticipated to be published in November or December 2015.

Discussion Points

Gina Mootrey corrected one statement. The WG already reviewed the safety and immunogenicity of Quadracel® during its May 2015 teleconference. No concerns arose with regard to Quadracel®. The hexavalent vaccine information will be presented to ACIP during the October 2015 meeting.

Human Papillomavirus (HPV) Vaccines

Introduction

Joseph A. Bocchini, Jr, MD
Chair, ACIP HPV Vaccine Work Group

Dr. Bocchini reminded everyone that the 9-valent HPV (9vHPV) vaccine was licensed by the FDA on December 10, 2014. This was considered by ACIP during the February 2015 meeting, which was shortened by the closure of CDC due to threat of inclement weather. During that time, ACIP did vote on the major issues related to the 9vHPV vaccine. The recommendations were published in an *MMWR Policy Note* published on March 27, 2015. The one issue that was not considered was additional vaccination for those who completed an HPV vaccination series.

Related to 9-valent HPV vaccine, the following presentations were made to ACIP over the past year:

- ❑ Epidemiology and burden of disease due to HPV types (February 2014)
- ❑ Clinical trial data (February 2014, June 2014, October 2014)
- ❑ GRADE (October 2014)
- ❑ Health economic analysis (October 2014, February 2015)
- ❑ Discussion of policy options (October 2014, February 2015)
- ❑ 9vHPV vaccine recommendations and vote (February 2015)

The HPV WG continued to meet subsequent to the February 2015 meeting and reviewed evidence for additional 9vHPV vaccination regarding type-specific disease, clinical trial data, and cost-effectiveness data; and discussed additional transition issues that have occurred since licensure of the vaccine; and have discussed considerations for guidance for providers.

During this session, presentations were given on the following topics:

- ❑ 9vHPV vaccination for persons who have completed an HPV vaccination series
- ❑ Impact and cost-effectiveness of additional vaccination
- ❑ Proposed guidance

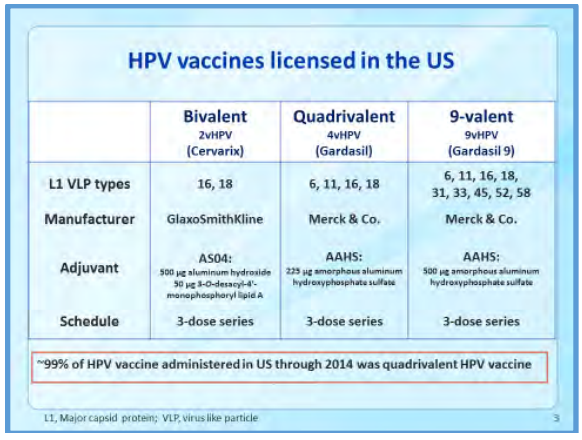
9-Valent HPV Vaccination for Persons Who Have Completed an HPV Vaccination Series

Lauri Markowitz, MD
HPV Vaccine Working Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Markowitz began by recognition of Dr. Bocchini's tenure on ACIP and as Chair of the HPV WG. He is rotating off of ACIP and stepping down as Chair of the HPV WG. He has served as Chair of the HPV WG since 2011, and has been a member of the WG since its inception in 2004. He has been an integral part of this WG. He was Chair of the WG for the vote to include males in the routine recommendation schedule for HPV and the vote for 9vHPV, so he has played a strategic leadership role. Even though Dr. Bocchini is stepping down as Chair, he will remain on the WG as a member.

During this session, Dr. Markowitz provided some background information including an overview of HPV vaccines, a review of the recommendations made in February 2015, and a discussion of issues related to program transition to 9vHPV vaccine. She then reviewed evidence related to the question of additional 9vHPV vaccination, type-specific attribution in cancers, and data from the one clinical trial of 9vHPV vaccine administered after a quadrivalent (4vHPV) vaccine series.

As a reminder, the three licensed US vaccines are listed in the following table:



All three are virus-like particle (VLP) vaccines. The bivalent (2vHPV) vaccine targets the cancer-causing types 16/18. The quadrivalent vaccine targets types 16/18 and types 6/11 that cause genital warts. The 9vHPV vaccine targets the same 4 types as the quadrivalent, as well as 5 additional cancer-causing types. The adjuvant differs between the 2vHPV and the 4vHPV and 9vHPV. Of note, about 99% of HPV vaccine administered in the US through 2014 was quadrivalent HPV vaccine.

As noted earlier, the 9vHPV vaccine was licensed in the US in December 2014. It was recommended by ACIP in February 2015, and an *MMWR Policy Note* was published at the end of March. Updated AAP vaccine recommendations now available in the 2015 Red Book are consistent with the February 2015 ACIP recommendations.

While the 4vHPV vaccine is licensed for females and males aged 9 through 26 years, the 9vHPV vaccine currently is licensed for males only through age 15. At the time of the first application to FDA, 9vHPV immunogenicity trials in males 16 through 26 years had not been completed. However, immunogenicity data for males 16 through 26 years were presented to ACIP in October 2014 and were later submitted to FDA. In February 2015, ACIP recommended use of 9vHPV in the currently recommended age groups and through 21 years for males. However, 9vHPV use in males 16 through 26 years is currently off-label.

The February 2015 recommendations that are now in the *Policy Note* state that routine vaccination is recommended at age 11 or 12 years with a 3-dose series. Vaccination is recommended through age 26 for females and through age 21 for males not previously vaccinated. Vaccination is recommended for men who have sex with men (MSM) and immunocompromised men through age 26. Vaccination of females is recommended with 2vHPV, 4vHPV, or 9vHPV. Vaccination of males is recommended with 4vHPV or 9vHPV. ACIP recommendations also state the following:

> If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, for protection against HPV 16 and 18, any HPV vaccine product may be used to continue or complete the series for females; 4vHPV or 9vHPV may be used to continue or complete the series for males.

Regarding programmatic issues related to the transition from 4vHPV to 9vHPV, following licensure of 9vHPV and the ACIP recommendation, 9vHPV was included in the VFC contract in April 2015. The contract price is $134 per dose, which is about $13 more than the contract price for 4vHPV vaccine. In May, the first time ordering of 9vHPV was possible on the VFC contract, just over 50% of awardees had placed orders that included 9vHPV. According to information from the manufacturer, as of June 2015, over 85% of managed care plans have decided to cover 9vHPV vaccine. Also of note, Merck intends to maintain 4vHPV in the US market until 9vHPV is approved by FDA for use in males 16 through 26 years and 6 months have passed from FDA approval of the male 16 through 26 year indication. Because of this, 4vHPV vaccine is expected to be on the market until mid-2016 pending FDA approval of the male 16 through 26 year indication.

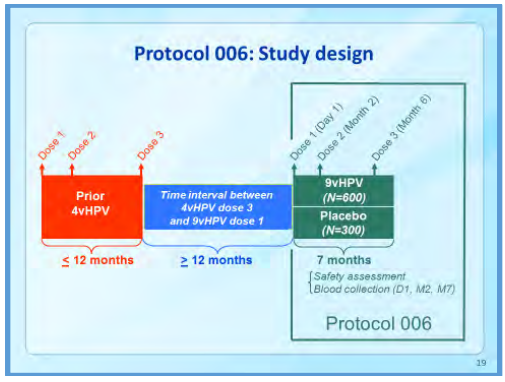
CDC has provided some suggestions to awardees to assist with implementation during the transition from 4vHPV to 9vHPV vaccine. Providers who have 4vHPV vaccine in stock but prefer to vaccinate their VFC patients with 9vHPV vaccine should be able to order 9vHPV vaccine. For those providers who choose to implement 9vHPVvaccine but still have 4vHPV vaccine stock, doses of 4vHPV vaccine can be used to complete the series for patients who started a series with 4vHPV vaccine, or can be used in males since the additional protection from 9vHPV will mostly benefit females.

The question of additional 9vHPV vaccine for persons who completed an HPV vaccination series was not discussed in February 2015 due to the abbreviated meeting. The *MMWR Policy Note* does not include information on this topic. There is no indication for additional 9vHPV vaccination in the vaccine label, although data are included in the label from the one clinical trial that addresses this issue. Additional 9vHPV vaccination has been a common question from vaccination providers and parents before and after 9vHPV vaccine licensure.

As presented to ACIP last year, there is variation in the percent of cancers attributable to any HPV by anatomic site, ranging from 63% to over 90%. The majority of cancers at all sites are attributable to HPV 16/18, ranging from 48% to 80%. The percent attributable to the 5 additional types in the 9vHPV vaccine ranges from a low of 4% for oropharyngeal cancers in males to 18% of vaginal cancers, one of the less common HPV-associated cancers[1]. Data pertaining to the estimated annual number of cancers attributable to HPV 16/18 and the 5 additional 9vHPV types are generated from the Saraiya study and the annual number of cases obtained from cancer registries. The majority of cancers that are attributable to HPV are attributable to HPV 16 and 18 at all anatomic sites. The largest number of cases due to the 5 additional types are cervical cancers[2] [[1]Saraiya et al. JNCI 2015;107; [2]Based on years 2006-2010 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a11.htm and data from Saraiya et al. JNCI 2015;107].

In the US, approximately 64% of HPV-associated cancers are thought to be attributable to HPV 16 or 18. HPV 16 or 18 account for 66% of cervical cancers and for the other cancers ranging from 48% penile cancers and 80% anal cancers. Of the HPV-associated cancers, 10% are attributable to the five additional types in 9vHPV (HPV 31, 33, 45, 52, 58). Of cervical cancers, 15% are attributed to these types with a range of 4% oropharyngeal to 18% vaginal. Due to the differences in the percent of cancers attributed to HPV types at the anatomic sites, there are differences by sex. The 5 additional types account for about 14% for HPV-associated cancers in females and only about 4% for males. For cervical pre-cancer lesions of cervical intraepithelial neoplasia (CIN)2 or worse, approximately 50% are caused by HPV 16 or 18 and 25% by the five additional types [*MMWR* 2015;64:300-4; *MMWR* RR 2014;63:1-30; Hariri et al. CEBP 2015;393-9].

ACIP reviewed data from the 9vHPV clinical development program during multiple meetings in 2014. The 9-valent clinical development program included the pivotal efficacy trial; immunogenicity/immunobridging trials; concomitant use trials; and 9vHPV among females who were previously vaccinated with quadrivalent HPV vaccine (Protocol 006). The objectives of the Protocol 006 trial were to evaluate the safety of 9vHPV in prior 4vHPV recipients and to evaluate the immunogenicity of 9vHPV with respect to HPV 31, 33, 45, 52, 58 in prior 4vHPV recipients. There were 924 females in the study, which was a double-blind RCT. Vaccine was administered on a 0, 2, 6 month schedule. Antibody was measured at enrollment post-dose 1 and post-dose 3. Although this study was conducted and that data were submitted to FDA, the manufacturer did not seek an indication for 9vHV vaccine among those previously vaccinated. The following graphic shows the study design, with the prior 3 doses of 4vHPV. There were at least 12 months between the last dose of 4vHPV and the first dose of 9vHPV in the study protocol. The green area shows Protocol 006 with the doses administered on a 0, 2, 6 month schedule:



The findings of Protocol 006 were presented to ACIP last year. Post-dose 1, seropositivity to types 31, 33, 45, 52, and 58 was 98%, 95%, 68%, 94%, and 99% respectively. Of course, all of these were revaccinated and there is no information on persistence of antibody after this one dose. Sera were not collected post-dose 2. Post-dose 3, over 98% of prior 4vHPV recipients were seropositive to all 5 types. In terms of the GMTs, for the types in the 4vHPV vaccine (6, 11, 16, 18) there was an increase in antibody post-dose 1 and no further increase after the third 9vHPV dose. Remember, these individuals had already received 3 doses of quadrivalent vaccine targeting these 4 types. The GMTs for the 5 additional types appear lower than those for the 4 original types. Also, there was an increase in antibody after the third dose compared to after the first dose of 9vHPV vaccine. Except for type 31, the fold difference ranged from 2.3 to 6. Listed on the slide were the injection site and systemic AEs that were observed among recipients of 9vHPV vaccine and had a frequency of greater than 1%. There was one SAE assessed to be due to vaccine in each group, tonsillitis and migraine, and both of these resolved [http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf].

In order to further assess the results, data from Protocol 006 were also used in a cross study comparison. The objectives of this analysis were to compare the safety of the 9vHPV vaccine in prior 4vHPV vaccine recipients with 9vHPV vaccine in 4vHPV vaccine naïve females, and compare immunogenicity in the two groups. GMTs were lower in those who previously received 4vHPV vaccine, with a ratio between .3 and .6. [http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ ApprovedProducts/UCM429166.pd].

Regarding injection-site AEs days 1 to 5 following each dose in protocol 006 and those who received 9vHPV vaccine but were naïve to vaccine in other studies, there appears to be a higher percentage of erythema (42% versus 32%) and swelling (49% versus 38%) in those who had prior 4vHPV vaccination compared to naïve women.

In summary, an updated HPV vaccine *Policy Note* was published in March 2015 following the ACIP voted in February 2015. The 9vHPV vaccine was included in the VFC contract on April 1, 2015. The transition to 9vHPV in public and private sectors is ongoing. The manufacturer expects 4vHPV vaccine to be on the US market until mid-2016. One trial evaluated 9vHPV vaccine in prior 3-dose 4vHPV vaccine recipients. After 3 doses of 9vHPV vaccine, over 98% of prior 4vHPV vaccine recipients were seropositive to all additional 5 types and there was an acceptable safety profile. In a cross study comparison of 9vHPV vaccine in prior 4vHPV vaccine recipients, 3 doses of 9vHPV vaccine resulted in lower GMTs for the 5 additional types compared with 3 doses of 9vHPV in HPV vaccine naïve females. The clinical significance of this is unclear, as there is no immune correlate of protection. The safety profile was similar, with the exception of higher rates of injection site reactions.

Cost-Effectiveness of 9vHPV Vaccination for Persons Who Have Completed an HPV Vaccination Series

Harrell Chesson, PhD
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Chesson briefly reviewed the health economics presentation from the February ACIP meeting, at which time a summary of the three models of 9vHPV in US and the cost-effectiveness of routine 9vHPV vaccination versus routine 4vHPV vaccination were presented. The three models for 9vHPV in the US include the following:

- US HPV-ADVISE Model [Brisson et al]
  - → Based on published 9vHPV Canadian model, calibrated to fit US data

- Merck Model [Weiss, Pillsbury, Dasbach]
  - → Based on published 4vHPV model, expanded to include the additional types in 9vHPV

- Simplified Model [Chesson et al]
  - → Based on published 4vHPV model, expanded to include the additional types in 9vHPV

These models were used to estimate the cost-effectiveness of routine 9vHPV vaccination. The specific question the models addressed was, "What is the cost-effectiveness of a routine 9vHPV vaccination program for both sexes compared to a routine 4vHPV vaccination program for both sexes?"

The following table shows the cost-effectiveness estimates for routine 9vHPV vaccination in terms of the incremental cost per quality-adjusted life year (QALY) gained:

Model	Incremental Cost Per QALY Gained	
	No 4vHPV cross-protection	With 4vHPV cross-protection
HPV-ADVISE	< $0 (cost-saving)	< $0 (cost-saving)
Merck	< $0 (cost-saving)	Not reported
Simplified	< $0 (cost-saving)	$8,600

The results are shown for two scenarios, with and without cross-protection for the quadrivalent vaccine. In the scenario of cross-protection, the 4vHPV vaccine was assumed to provide partial protection against the additional five types in the 9vHPV. The first column of results is for the no cross-protection scenario, for which all models suggest that 9vHPV vaccination is cost-saving compared to routine 4vHPV vaccination. In the scenario of 4vHPV cross-protection, 4vHPV provided partial protection against the additional five types in 9vHPV and the cost per QALY gained is quite low at $0 in the HPV-ADVISE Model and under $10,000 in the Simplified Model.

To summarize the results already presented, the 9vHPV vaccine for both sexes compared to 4vHPV for both sexes is likely cost-saving. The cost per QALY gained is less than $0 in most scenarios examined, and this was true in all three models examined. The cost per QALY did not exceed $25,000 in the sensitivity analyses. Most of the incremental benefits of 9vHPV vaccine are due to vaccination of females.

In terms of the impact and cost-effectiveness of additional 9vHPV vaccination among prior 3-dose 4vHPV vaccinees, the same three models used to address routine vaccination were used to address the cost-effectiveness of additional 9vHPV vaccination. The specific question addressed was, "What is the cost-effectiveness of providing 3 doses of 9vHPV to females who were previously vaccinated with 3 doses of 4vHPV vaccine?" All three models assumed that females aged 13 through 18 who had been vaccinated with the 4vHPV vaccine would be eligible for additional 9vHPV vaccination. All three models also assumed that additional 9vHPV vaccination would be a temporary program that would take place in the context of an ongoing routine 9vHPV vaccination program for both sexes.

The following table shows the estimated impact and cost per QALY gained by additional 9vHPV vaccination:

Impact and cost per QALY gained by additional 9vHPV vaccination

Item estimated	HPV-ADVISE		Simplified	Merck
	No 4vHPV cross-protection	With 4vHPV cross-protection	No 4vHPV cross-protection	No 4vHPV cross-protection
Number of female 4vHPV recipients given additional 9vHPV	1,065,000	1,065,000	950,300	1,109,000
Incremental cost	$432 million	$420 million	$392 million	$390 million
Incremental gain in QALYs	3,700	2,500	2,700	2,500
Incremental cost per QALY gained by additional 9vHPV	$117,400	$170,600	$146,200	$156,100

QALY: quality-adjusted life year
Additional 9vHPV: providing 3 doses of 9vHPV to prior 3-dose recipients of 4vHPV

For example, for the HPV-ADVISE model, it was estimated that about 1 million females would receive additional vaccination at an incremental cost of $432 million with a gain in QALYs of 3,700. This works out to an incremental cost per QALY gained of about $117,000. The results for the other models are quite consistent with the results of the HPV-ADVISE model.

In terms of why routine 9vHPV vaccination is so much more cost-effective than additional 9vHPV vaccination, the incremental benefits are the same for routine and additional vaccination. That is, routine and additional 9vHPV vaccination both provide protection against the additional five types. The difference is in the incremental costs per person vaccinated. When switching from a routine 4vHPV program to a routine 9vHPV program, the incremental cost is simply the difference in the cost of the two vaccines or about $13 per dose. In contrast, the entire cost of the vaccine of $134 per dose is incurred to provide additional vaccination. Therefore, the difference in the incremental cost explains the difference in the cost-effectiveness of these two vaccination strategies.

Dr. Chesson presented results for sensitivity analyses from the HPV-ADVISE model, given that this model has performed the most extensive sensitivity analyses to date. The model accounts for uncertainty in the natural history by applying 50 different parameter sets. Each parameter set is run 40+ times. The results can differ from one model run to another due to chance, and 80% uncertainty intervals calculated from 10th and 90th percentiles of these simulations. Because chance effects are relatively large compared to the effects of the additional 9vHPV vaccine program effects, these uncertainty intervals should be interpreted with caution.

Regarding the cost-effectiveness of additional 9vHPV vaccination from the HPV-ADVISE model in terms of the cost per QALY gained, regardless of whether cross-protection is assumed for the 4vHPV vaccine, the cost per QALY gained for 9vHPV vaccination ranges from about $7,000 to infinity. These extremes are not believed to be particularly realistic. What is occurring is that chance fluctuations in the model simulations are making the additional vaccination appear to be a lot worse or a lot better than it actually is. The actual interval of realistic estimates is believed to be much narrower than this, but a determination has not yet been made about how to do this.

In summary, the cost per QALY gained by three doses of 9vHPV for prior 3-dose 4vHPV recipients is consistent across the three models at $117,400 in the HPV-ADVISE Model; $146,200 in the Simplified Model; and $156,100 in the Merck Model. As a reminder, these estimates are for the additional 9vHPV vaccination of females aged 13 through 18 years. The cost per QALY gained by additional 9vHPV vaccination would be higher for females over 18 years of age and males of any age.

In conclusion, routine 9vHPV vaccination for both sexes is likely to be cost-saving versus routine 4vHPV vaccination for both sexes. All three models also agree that additional 9vHPV vaccination would cost more than $100,000 per QALY gained. The cost-effectiveness could be even less favorable than estimated if, for example, it is possible to achieve higher routine 9vHPV vaccination coverage than assumed in the models or if the people who receive additional vaccinations are the same ones who receive cervical cancer screening.

Discussion Points

Dr. Schuchat announced that the Supreme Court issued a ruling 6 to 3 in favor of upholding the Affordable Care Act (ACA).

Dr. Karron noted that all of the economic models are based upon the necessity of three doses of the 9vHPV vaccine; however, she wondered what was known about one or two doses.

Dr. Markowitz replied that as discussed during two previous ACIP meetings, there is an ongoing trial of two doses of 9vHPV vaccine. That trial is fully enrolled and the data will be analyzed over the next four to six months, so those data will be forthcoming. The study will assess two doses administered at 0, 6 months and two doses administered at 0, 12 months in 9 through 14 year olds. That is being compared to a three-dose schedule in the age group that was in the efficacy trial. In protocol 006 (the trial of 3 doses of 9vHPV in persons who previously received 4vHPV), antibody was determined after dose 1 and dose 3, but not after dose 2. Also, there was no follow-up of individuals who received a single dose because they all received doses 2 and 3.

Dr. Reingold asked whether it was possible to estimate how many cancers at different sites would be prevented by administering an additional three doses of 9vHPV vaccine to a cohort of women who have received 4vHPV vaccine.

Dr. Chesson responded that this can be done and provided to ACIP.

Dr. Markowitz added that this is somewhat different and not as straightforward as it is for other vaccines, because the cancers occur far out. During that time, 9vHPV vaccine will be used in a routine program and there will be some herd protection from that.

Dr. Gemmill (NACI) reminded everyone that Canada uses a two-dose in some provinces, and their current dilemma regards what to do with the 9vHPV vaccine.

Given the current level of uptake of 4vHPV vaccine and 9vHPV vaccine in vaccine-naïve individuals, Dr. Temte wondered what the effect would be of spending $400 million per year to enhance vaccination of vaccine-naïve people. That is, would increasing the first dose in girls from 50% to 75% and achieving a higher rate of completion have much more effect than administering additional doses in terms of a stable amount of public expenditure? There remains a struggle to administer even one dose to half of the US population of either vaccine.

His fear is that programs to revaccinate people are going to target a group that is already getting the vaccine, and may not be the group that really needs to be vaccinated in the first place.

Dr. Chesson replied that the cost-effectiveness of additional 9vHPV vaccination compared to an intervention to increase coverage of routine 9vHPV vaccination could be modeled. He said his bet would be that the intervention to increase routine 9vHPV coverage could incur substantial program costs and still come out ahead of additional 9vHPV vaccination in terms of cost-effectiveness and impact.

Proposed Guidance

Lauri Markowitz, MD
HPV Vaccine Working Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

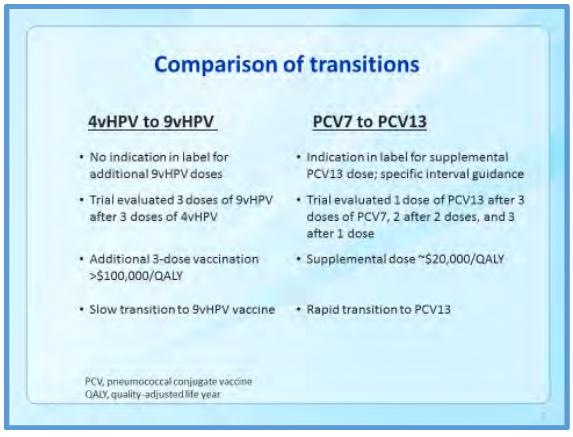
To summarize this session, evidence is from one RCT that evaluated the immunogenicity of 3 doses of 9vHPV vaccine versus placebo among prior 3-dose 4vHPV vaccinees. After the third dose, seropositivity for all 5 additional types was over 98%. There has been no formal non-inferiority immunobridging evaluation. However, in a cross study comparison, the GMTs for the 5 additional types after 3 doses were lower than those after 3 doses of 9vHPV vaccine in HPV vaccine naïve women. The clinical significance of the lower titers is not known, because there is no immune correlate of protection. No safety concerns are apparent. In the cross study comparison, there were higher rates of injection site reactions compared with 9vHPV vaccine in HPV vaccine naïve females.

The benefit of protection against the 5 additional types would be mainly for females for the prevention of cervical cancers and precancers. The cost per QALY gained is over $100,000 for the additional 3 doses among females 13 through 18 years of age. There is a higher cost per QALY for females over age 18 years, and for males at any age. In contrast, the models have shown that routine 9vHPV vaccination for females and males in the US is cost-saving compared to a quadrivalent HPV vaccination program.

The WG felt that the highest priority was raising 9vHPV vaccine coverage for the primary vaccination series. A variety of programmatic issues were considered for routine and additional vaccination. As was mentioned and most ACIP members know, 2013 coverage for 13 through 17 year olds for one dose was approximately 57% and for three doses 38%. So, a lot of work has to be done to raise coverage in the US. The economic analyses and considerations reviewed varied. Some WG members placed more weight on the health economic analyses than others. The WG also noted that cervical cancer screening continues to be recommended for women aged 21 through 65 for vaccinated and unvaccinated women.

The WG members were not in favor of a recommendation for routine additional 9vHPV vaccination of persons who previously completed a 3-dose HPV vaccination series. However, it was felt that guidance and information are needed in a variety of areas. First, although some recommendations are provided in the *Policy Note* for persons who started the series with another vaccine, further guidance has been requested by vaccination providers since recommendations were published. Second, for persons who completed a 3-dose HPV vaccination series, WG members felt that clarification is needed regarding what data are and are not available.

As mentioned earlier, questions about additional vaccination have been common, both before and after licensure. Some parents and providers are interested in additional protection against the 5 additional types. Some parents and providers may be just seeking information and guidance. The WG felt this was partly because of provider recall regarding the pneumococcal conjugate vaccine (PCV) 7 to 13 transition, but there are differences between that transition and the HPV vaccine transition as reflected in the following comparison:



There are no plans for an additional HPV vaccine *Policy Note* in the *MMWR* with this guidance. Instead, information will be posted on the CDC website. There will be a link from the ACIP website recommendation page to this information, as well as a notice in the *MMWR* with a link to this information. Examples of guidance for providers has been drafted for three areas: 1) 9vHPV vaccination for persons who started the series with another HPV vaccine product; 2) 9vHPV vaccination for persons who completed an HPV vaccination series; and 3) 9vHPV vaccination and information available.

Example 1: Vaccination for Persons Who Started the Series with Another Vaccine Product

If a series was started with quadrivalent HPV vaccine or bivalent HPV vaccine, can it be completed with 9-valent HPV vaccine?

- Yes, ACIP recommendations state that 9-valent HPV vaccine may be used to continue or complete a series started with a different HPV vaccine product.

Are additional 9-valent HPV vaccine doses recommended after a series started with quadrivalent or bivalent HPV vaccine and completed with 9-valent HPV vaccine?

- There is no ACIP recommendation for additional 9-valent HPV vaccine doses for persons who started the series with quadrivalent or bivalent HPV vaccine and completed the 3-dose series with 9-valent HPV vaccine.

If a series was started with quadrivalent HPV vaccine or bivalent HPV vaccine and will be completed with 9-valent* HPV vaccine, what are the intervals for the remaining doses in *the 3-dose series?

- The current recommended HPV vaccination schedule is for the second dose to be given 2 months after the first dose and the third dose 4 months after the second dose (6 months after the first dose). ACIP does not state maximum intervals between HPV doses.

- Antibody titers have not been found to be diminished after longer than standard intervals between doses. Data from other HPV vaccine studies show equal or higher antibody titers when 2 doses were administered at an interval of 6 months compared with 2 months.
  - An ongoing immunogenicity study is evaluating 2 doses of 9-valent HPV vaccine separated by an interval of 6 or 12 months.

Example 2: Vaccination for Persons Who Completed an HPV Vaccination Series

Is additional vaccination with 9-valent HPV vaccine recommended for persons who have completed a 3-dose series of either quadrivalent or bivalent HPV vaccine?

- There is no ACIP recommendation for routine additional 9-valent HPV vaccination of persons who previously completed a quadrivalent or bivalent vaccination series.

If a person desires protection against the 5 additional types prevented by the 9-valent HPV vaccine and has completed a 3-dose series of HPV vaccine, what issues should be considered?

- The benefit of protection against the 5 additional types targeted by 9-valent HPV vaccination is mostly limited to females for prevention of cervical cancers and precancers. This is because only a small percentage of HPV associated cancers in males is due to the 5 additional types in 9-valent HPV vaccine.

- Available data show no serious safety concerns in persons who were vaccinated with 9-valent HPV vaccine after having received quadrivalent HPV vaccine.

- Cervical cancer screening is recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women.

Example 3: Information Available

What data are available on efficacy and immunogenicity of 9-valent HPV vaccination for the 5 additional types, when administered after a complete 3-dose series of another HPV vaccine product?

- In the one immunogenicity trial, 3 doses of 9-valent HPV vaccine vaccination (on a 0,2,6 month schedule) were given to females who had completed a 3-dose quadrivalent HPV vaccine series; the first dose of 9-valent HPV vaccine was administered at least 12 months after completion of the quadrivalent vaccine series.
  - After 3 doses of 9-valent vaccine, over 98% of vaccinees developed antibody to all 5 additional types. Antibody was also measured after the first dose of 9-

valent HPV vaccine; most but not all vaccinees developed antibody against all 5 additional types. Antibody was not measured after the second dose.

- In a cross study comparison, geometric antibody titers for the 5 additional types after 3 doses of 9-valent HPV vaccine were lower, 25-63% of those in persons who received 3 doses of 9-valent HPV vaccine without prior HPV vaccination. The significance of the lower antibody titers is not known because there is no immune correlate of protection.

What data are available on safety of 9-valent HPV vaccination when administered after a complete 3-dose series of another HPV vaccine product?

- In a randomized trial, 9-valent HPV vaccine was compared with placebo in females aged 12-26 years who had previously received 3 doses of quadrivalent HPV vaccine. Among the 608 who received 9-valent HPV vaccine, there was an acceptable safety profile.

- Compared to persons in other studies who were vaccinated with 9-valent HPV vaccine without prior HPV vaccination, those who received 9-valent HPV vaccine after a 3-dose quadrivalent vaccine series had higher rates of injection site swelling and redness.

- Otherwise, the safety profiles of 9-valent vaccine given to HPV vaccine naïve persons and of 9-valent vaccine given to persons who had previously completed a 3-dose series were generally similar.

Discussion Points

Dr. Middleman (SAHM) noted that SAHM's major concern pertained to ensuring that there is no discrepancy for those who would like to be revaccinated in terms of those who can and cannot afford to do so. She assumed that it would be covered by the VFC since it is approved, but she was curious to know from insurance companies what their policies might be.

Dr. Netoskie (AHIP) said his understanding was that a three-dose series would be covered regardless of the combination. If ACIP made no recommendation and it offered no significant additional advantage, he assumed the cost would be the responsibility of the patient.

Dr. Orenstein (NVAC) said that was his concern as well. The way he read it, one would have to pay out-of-pocket for revaccination. Based on the data presented, it appeared that about 3000 cancer cases might be preventable. Cancer has been one of the major concerns. In his opinion, there should be at least a Category B recommendation.

Dr. Kimberlin (AAP) reported that families and pediatricians are already asking this question. He thought the AAP would need to provide some guidance. If there is no recommendation but there is information to show that the vaccine is safe and adds some degree of efficacy, those would can afford it will get it and those who cannot will not get it. Whereas, a Category B recommendation from ACIP would tie in those funds and would equalize the potential discrepancy. The AAP would be interested in working with the WG to develop such language if the ACIP is interested.

Dr. Moore (AIM) added her voice to the suggestion that the WG and ACIP consider a Category B recommendation. Especially in light of the discussions and numbers from the previous day, these numbers seem rather favorable in terms of the volume of cancer cases that could be

prevented. Although not as sudden and dramatic as “out of the blue” deaths, these are agonizing deaths for families of young adults throughout the country. If there are those who wish to avail themselves of additional safe protection to prevent that risk even further, that opportunity should be made available to them.

Dr. Fryhofer (AMA/ACP) thought the guidance statement would be very helpful for practitioners, and wondered when it would be posted on the website.

Dr. Markowitz thought the guidance could be placed on the website in a matter of weeks, although it will take longer for the announcement in the *MMWR*.

Dr. Harrison asked whether the WG discussed the plusses and minuses of a Category B recommendation, and if so, if she could summarize the discussion.

Dr. Markowitz replied that they did, and a GRADE analysis was conducted as well. Some WG members favored a Category B recommendations and some did not.

Dr. Ault (ACOG) noted that Dr. Chesson had a publication in the past couple of years that stated that about $6 billion is spent on HPV and related cancers, while approximately $5 billion is spent on screening for cervical. He wondered whether that was also in the model.

Dr. Chesson responded that the models do take into account the vaccines’ effect on reducing the costs associated with screening, and assume that cervical cancer screening will continue into the future.

With all due respect to trying to eliminate as much cancer as possible, Dr. Riley thought if all of the time, energy, funds, and time were focused on vaccinating more young girls and boys, the results might be much better. She feels very strongly that spending a lot of energy on the population that has already been fully vaccinated diverts attention. Many efforts have been made only to achieve a 50% vaccination rate among the eligible population. Putting the effort into vaccination of a much greater number of people will make a major difference.

Dr. Belongia pointed out that applying more generally the equity issue and the fact that there is some benefit to receiving additional doses of 9vHPV, a logical conclusion could be reached that every vaccine licensed by the FDA should at least get a Category B recommendation because they are safe and effective.

Dr. Middleman (SAHM) echoed that SAHM supports the recommendation of immunization with one kind or another. They want the focus on getting everyone immunized at least once. Their concern is the equity concern and ensuring that there is not a disparity when some patients truly want to be revaccinated. They are not suggesting that the focus move to revaccination. They are simply suggesting that it be an option available to those who desire it.

Dr. Harrison said his point regarded whether it was a zero sum game. He fully recognized that uptake was poor. However, he wondered whether a Category B recommendation would divert attention away from the focus of putting the effort into vaccination of a much greater number of people with one vaccine.

Dr. Baker (IDSA) said she understood lack of consensus in a WG, recognizing that this was sometimes because there were not enough data. She wondered whether Dr. Markowitz anticipated that the 2-dose data that would be available by October would help the discussion.

Dr. Markowitz said while she was hopeful the data would be available in October 2015 regarding the 2-dose trial, she was not 100% sure that they will be available at that time. Enrollment is complete, but they have not been given a guarantee that they will see those data in October. It might be February 2016, at the latest. While those data will be helpful, they are not specifically relevant to the additional vaccination question because they are in vaccine naïve individuals. It is known that antibody titers are lower in people who have received 9vHPV vaccine after 4vHPV vaccine. Also important to note is that all of the data on 2 doses, including the one quadrivalent vaccine trial from Canada are just for 9 through 14 year olds.
Regarding equity, Dr. Sawyer (PIDS) thought that VFC providers could administer as many vaccines as they wished as long as there is no recommendation. For example, could they give 10 MMRs and have all of them covered by VFC?

Dr. Moore (AIM) indicated that AIM runs the VFC program in Tennessee and they do not count the number of doses being given. Practitioners just tell them how many doses they need to order. This is not cross-checked with individual patients to determine whether the required number of doses are given to each patient. If this was done all of the time and someone reported a physician, they might have to have a conversation about it.

Dr. Bennett said she was very sensitivity to the equity issue, and this reminded her of the Virginia Slims "You've Come a Long Way Baby" advertisements. That was about equity and smoking. It seemed to her that the WG had determined that giving additional doses is not valuable. She did not believe they should be worrying about equity for something they did not believe to be the right thing to do.

It seemed to Dr. Temte that it might be best for the WG to consider this further, given the divided interest in a Category B recommendation.

Dr. Schuchat pointed out that the FDA approval of the 9vHPV vaccination was not for the indication of revaccination. The transition plans are going to be somewhat prolonged compared to the transition with the PCV7/13 swap out. CDC views implementation guidance differently from ACIP policy. CDC envisions implementation guidance in terms of states ordering as the agency's responsibility, so the idea is to post commonly asked questions and answers in this transitional period. This is not even an FDA-approved indication. This is simply a commonly asked questions from clinicians and programs. The goal is to disseminate information about the evidence, as well as practical answers to the questions being posed.

Dr. Bocchini clarified the WG deliberations, pointing out that 9vHPV vaccine clearly has benefits and that was not in question. They key issues related to strong opinions in the WG regarding whether a focus on revaccination would impede the primary purpose to get people vaccinated in the first place. There are strong opinions on both sides. If the February 2015 meeting had not been truncated, the session would have included information of doing one or the other based on the GRADE analysis and showing ACIP that there were differences of opinion among WG members about this in order to ask ACIP to weigh in on a Category B recommendation. It is certainly reasonable for the WG to provide that additional information to help ACIP make that decision.

Dr. Rubin pointed out that the two are not mutually exclusive. Guidance could be provided and subsequently, a decision on a Category B recommendation could be made.

Dr. Temte thought the intent was for the guidance to be provided. As a clinician, he said he found everything CDC develops to be very helpful. The question regarded whether the members felt that additional time and effort should be put into make a decision about a Category B recommendation, although ACIP tries desperately not to use Category B recommendations very often.

In terms of process, Dr. Campos-Outcalt wondered what the result of doing nothing during this session would be.

Dr. Temte pointed out that for zoster vaccine, there was no vote on anticipation of changing the age. For Tdap, there was no vote on consideration of revaccination. By not taking a vote, ACIP confirmed current policy for those decisions. By not taking a vote during this session, they would affirm the fact that ACIP recommends one of the three vaccines available, with no preference expressed for any one of the vaccines. They would also not go beyond the FDA licensure in terms of promoting revaccination.

Dr. Campos-Outcalt asked whether those not in agreement with the current statement needed to make a motion to send it back to the WG, or make a motion to make it a Category B recommendation. Otherwise, it would stand as proposed.

Dr. Markowitz clarified that there is no ACIP recommendation for routine additional vaccination. The guidance language also addresses what needs to be considered if someone does want additional protection. This was included to let people know the safety data available and that for males, there is little additional protection.

Dr. Harrison favored further discussion about the possibility of a Category B recommendation, reiterating the concern about whether a Category B recommendation may have a negative effect on the efforts to get naïve people vaccinated with the first series.

Dr. Schuchat pointed out the importance for ACIP members to remember that whatever they decided to do during this session, they would not get rid of HPV. Additional deliberations and WG recommendations are anticipated in October or February regarding the number of doses and interval issues. The question of what constitutes revaccination is probably related to what constitutes primary vaccination. She appreciated the support for guidance during this transition period, with all vaccine products available and the number of people who have received one or two doses of what is currently recommended to be a three-dose series. ACIP is likely to be asked in the future about alternative intervals, alternative numbers of doses, and possibly differences by age. In terms of revaccination, there are many permutations for clinicians to absorb. ACIP will have to revisit the topic of HPV vaccination recommendations in the future.

Lynn Bahta (Minnesota Department of Health) noted that in February 2015, ACIP voted to recommend either 2-valent, 4-valent, or 9-valent vaccination. Suddenly, they are now concerned that they cannot administer revaccination for 9-valent. That would suggest to everyone that they were inadequately vaccinated for 2-valent or 4-valent. That is the indirect message in having this conversation.

Dr. Temte emphasized that ACIP's current policy does not express a preference.

Dr. Hahn (CSTE) pointed out that as the parent of an 11-year old girl, she is going to make sure that her child receives the 9-valent and feels that they are in an odd position to be talking about this conundrum. Few people are starting on the 4-valent based on current recommendations at

this point. In terms of the guidance, perhaps a question should be added for naïve persons in terms of emphasizing that most young children should be started on the 9-valent vaccine.

Dr. Markowitz agreed that the transition from 4-valent to 9-valent is a very awkward position to be in, and not all providers have 9-valent vaccine. The transition is not going to be immediate. The program has been leery to tell providers to delay vaccination. The way to solve this is to get 9-valent vaccine into offices quickly to make sure that it is available.

Dr. Hahn (CSTE) noted that with influenza vaccine, language was used to say that if an office had both, one should be used preferentially in certain situations. Perhaps this would be a way to address the transition.

Dr. Lett (Massachusetts) indicated that Massachusetts made a quick transition, and she heard that there was ample 9-valent vaccine available for ordering. She requested that the manufacturers offer clarification about that.

Dr. Campos-Outcalt added that this occurred previously with the transition from PCV7 to PCV13, in which case, the manufacturer agreed to exchange the vaccines. He wondered whether that same arrangement had been made with regard to HPV vaccine.

Kathy Garrett (Merck) indicated that Merck has no current supply issues, so the vaccine is available. They do not have an exchange program available at this time.

Dr. Schaffner (NFID) asked why there is no exchange program available.

Kathy Garrett (Merck) responded that Merck's expectation is that since there is not currently an indication for males above the age of 15, the 4-valent vaccine can be used to begin or complete the series among males.

Regarding modeling, Dr. Riley wondered what would happen to the 3000 cervical cancers if primary vaccination of a greater percentage of the population was more successful.

Dr. Chesson responded that they could assess different scenarios of routine vaccination coverage and additional vaccination coverage to explore the trade-offs and implications for cervical and other cancers.

It did not seem to Dr. Harriman that one negated the other. Everybody's efforts could still go into getting people vaccinated with the primary series, and those interested in being revaccinated could be. To her, it did not seem that one would supplant or affect that other.

Dr. Schuchat clarified that 3000 cervical cancers were not among those who had received three doses of quadrivalent 20 years earlier. That is the total universe, and she did not think that was a number on which to focus.

Dr. Kempe thought there were some issues regarding how making a Category B recommendation could affect the receipt of 9-valent vaccine among those who are unimmunized. It is likely to send an important message to programs and physicians that it becomes much more of a priority to revaccinate with the 9-valent vaccine. It really comes down to coverage. The guidelines already say that it is beneficial and that practitioners should use individual discretion, but the issue is to ensure that there is not inequity in coverage. There is

reason to think that a Category B recommendation does affect the way physicians, organizations, and system will deliver the program.

Dr. Belongia thought the issue regarded whether equity could come at the expense of the potential for a Category B recommendation to lead to more of a focus on additional vaccinations of people who have already completed a primary series beyond what ACIP intended, rather than vaccination of people who need the primary series.

Dr. Temte said he heard a lot of interest from the liaisons in the possibility of a Category B recommendation, and it was somewhat more equivocal among the ACIP members. He suggested that this go back to the HPV WG for further consideration at this point.

Dr. Bocchini said he thought the WG would be happy to provide additional information and work through the pros and cons of a Category B recommendation, so that all of the data would be before the ACIP to help make that decision.

Dr. Temte stressed that the intent was to provide the guidance on the website in the interim for clinicians. He thought that the strong message should be to emphasize that the important thing is initial use of one of the three vaccines and expanding coverage, as that is where the true benefit lies.

Dr. Schuchat pointed out that if this was going to be taken back to the WG, the WG probably also needed to reassess what should be done about preference among the licensed products.

Dr. Markowitz indicated that they would move forward with putting the guidance on the website, and taking these issues back to the WG.

Pertussis

Introduction

Art Reingold, MD
Chair, ACIP Pertussis Vaccine Work Group

Dr. Reingold reminded everyone that the terms of reference for the Pertussis Vaccine WG are to:

- Review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate them into a single statement.

- Review new data on Tdap including
  - Effectiveness of ACIP recommendations
  - Interval between Td booster and Tdap
  - Use of Tdap in adults ages 65 years and older
  - Pregnant and breastfeeding women
    - Use of Tdap
    - Cocooning strategies
  - Vaccinated HCP and need for post-exposure prophylaxis

  - Tdap revaccination
    - Pregnant women
    - Healthcare personnel
    - "Cocooning"

- Review updated epidemiology of tetanus and diphtheria in the US

Two Tdap products are licensed in the US, both of which are licensed for single use. GSK's BOOSTRIX® vaccine has an age indication of 10 years and older, while Sanofi Pasteur's ADACEL™ vaccine has an age indication of 10 through 64 years of age. The current ACIP recommendations is for a single Tdap dose for all persons aged 11 years and older, with preferred administration at 11 or 12 years of age. Pregnant women are recommended to receive a dose of Tdap with every pregnancy. This is primarily designed to provide protection to the newborn baby. A decennial Td booster is recommended for those who have received 1 Tdap vaccine, and a booster is recommended at 5 years for wound management. Diphtheria, tetanus, and acellular pertussis (DTaP) vaccine coverage among children is high and adolescent Tdap coverage has greatly improved; however, adult Tdap coverage remained low at 14% as of 2012.

Administering Tdap to pregnant women raises safety concerns. There have been 69 Tdap reports in pregnant women to the Vaccine Adverse Event Reporting System (VAERS) since the last ACIP update in February 2014. Tdap had been given during the third trimester in 15 of 21 of the reports with data on gestational age at time of vaccination. The conditions among the 69 reports included no AE (35), injection site reaction/shoulder or arm pain (19), stillbirth (5), systemic reactions (3), Guillain-Barré Syndrome (GBS) (2), anaphylaxis allergic reaction (2), abdominal pain (1), multiple allergies (1), contractions/unspecified (1). No safety signals have been identified in ongoing monitoring. There was a presentation during a prior ACIP meeting concerning a possible relationship between Tdap vaccination and an increased risk chorioamnionitis. Additional analyses are in progress concerning chorioamnionitis, and there is a Clinical Immunization Safety Assessment (CISA) Project underway that is a prospective observational clinical study of Tdap safety in pregnant women (ClinicalTrials.gov NCT02209623).

In June 2013, ACIP concluded that the public health impact of routinely recommending a second dose of Tdap would be limited, and that no change should be made to the current Tdap recommendation. ACIP recognized that the focus should be on preventing pertussis in infants, and ensuring that pregnant women receive Tdap during each pregnancy. ACIP supported the WG to consider additional doses for special populations, including HCP and close contacts of infants. In October 2014, ACIP concluded that there is no supportive evidence to suggest that additional doses would be beneficial in prevention of disease and transmission in a health-care setting and no change was made to the current ACIP Tdap recommendation for HCP.

This session included presentations on Cocooning and Tdap vaccination, and acellular pertussis vaccine effectiveness among children and adolescents in the setting of pertactin-deficient B. pertussis in Vermont from 2011 through 2013.

"Cocooning" and Tdap Vaccination

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As Dr. Reingold noted, Dr. Liang reminded everyone that ACIP made considerations for a second dose of Tdap for the general population and healthcare personnel (HCP) but did not change the current recommendations. The WG has since considered Tdap vaccination of close contacts of infants, and evaluated the need for and potential benefit and impact of additional doses. During this session, Dr. Liang presented a summary of these data and the WG's conclusions. The following information was presented to ACIP in October 2014 when reviewing considerations for HCP. As a reminder, currently both Tdap vaccines are licensed only for a single dose.

A second dose of Tdap is safe and immunogenic. There are several published clinical trials from other countries on a second dose of Tdap at 5 or 10 year after the first dose. Reported AEs were generally comparable to those after the first Tdap. The majority of local and systemic AEs were mild to moderate and self-limited. Of the few SAEs reported, none were determined to be related to receipt of the second Tdap. Safety profiles were comparable at the 5- and 10-year intervals. For immunogenicity, after a second Tdap, tetanus and diphtheria seroprotection were close to 100%. For pertussis vaccine components, responses are similar at the 5- and 10-year intervals. Responses are also comparable to historic and contemporaneous first dose [Halperin 2011; Knuf 2010; Booy 2010, Halperin 2012, Mertsola 2010].

In the US, both pharmaceutical companies are conducting clinical trials of a second dose of Tdap. Sanofi Pasteur's US study for a second dose of ADACEL™ is complete and was presented to ACIP in 2013. A revaccination study in Canada will finish later this year and Sanofi Pasteur plans to submit the results to the FDA for consideration of label updates. GSK is conducting clinical studies in the US for revaccination after prior vaccination with BOOSTRIX®. GSK recently completed a revaccination study of young adults 20 through 28 years of age who were initially vaccinated 10 years earlier when they were adolescents 11 through 18 years of age. A revaccination study in adults 28 through 73 years old who were initially vaccinated approximately 9 years ago, when they were 19 through 64 years old, began this year. Plans to submit the data to the FDA for consideration of a label update for BOOSTRIX® will be dependent on pertussis epidemiology and ACIP recommendations.

With regard to Tdap vaccine effectiveness, previous estimates range between 66% and 78%. However, these studies involved adolescents who received some whole cell vaccines as part of their childhood series. At the time, the effectiveness of Tdap among adolescents who had received only acellular vaccines in childhood was unknown. In 2012, in collaboration with Washington State Department of Health, CDC conducted a large-scale study in adolescents who only received acellular pertussis vaccines as part of their childhood series. Estimated Tdap vaccine effectiveness was 65% and is consistent with previous studies. This study also assessed the duration of protection [Rank C, et al. Pediatr Infect Dis J. 2009 28(2):152-3; Wei

SC, et al. CID 2010 51(3):315-321; Skoff et al. NIC 2011, Washington, DC; Acosta A, et al. Pediatrics 2015 135(6)].

In 2012, Wisconsin also evaluated Tdap vaccine effectiveness and duration of protection in their adolescent population who received only acellular vaccines. Despite different methodologies, both studies showed Tdap to be effective, but that effectiveness decreases with increasing time since receipt [[1]Acosta et al. Tdap Vaccine Effectiveness and Duration of Protection Among Adolescents During the 2012 Washington State Pertussis Epidemic. Pediatrics 2015 135(6); [2]Koepke et al. Estimating the Effectiveness of Tdap Vaccine for Preventing Pertussis: Evidence of Rapidly Waning Immunity and Differences in Effectiveness by Tdap Brand. The Journal of Infectious Diseases 2014].

For indirect protection, it is unclear what the effect of Tdap vaccination is on preventing pertussis transmission. For people vaccinated with acellular pertussis vaccines, symptoms are not as severe and are presumably less likely to transmit. An Australian cocooning case-control study found a modest decrease in the risk of pertussis in infants whose parents were vaccinated at a sufficient time to boost their immune response relative to the infant pertussis incubation period. This effect was also seen in infants whose mothers were vaccinated post-partum. But it is unclear whether the lower risk for infants was attributable to a short-term impact on transmission for recently vaccinated mothers *or* lack of exposure. An animal model showed that acellular pertussis vaccinated baboons were protected against disease but not infection. Bacterial colony counts from nasopharyngeal washes were comparable to those observed in unvaccinated animals. Infected but asymptomatic baboons transmitted pertussis to other cohoused baboons. Although these results are striking, it is unclear if this animal model represents what happens with humans, vaccines, and infection. There is currently no human challenge model [[1]Quinn HE et al. Parental Tdap boosters and infant pertussis: a case-control study. Pediatrics. 2014 Oct;134(4):713-20; [2]Warfel JM et al. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. 2014 Jan 14;111(2):787-92].

Compared with other age groups, infants less than one year of age have the highest reported incidence of pertussis compared to other age groups, with incidence ranging from 27 to 127 cases per 100,000. Young infants have serious pertussis-related complications. Among all infant pertussis cases, infants 2 months of age or younger have the highest reported percent of hospitalizations and deaths [2014 data are provisional and subject to change; Source: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System].

When Tdap was first recommended in 2005, ACIP recommended a dose of Tdap for close contacts of infants. This “cocooning” strategy would protect the vaccinated individual from pertussis and potentially provide indirect protection to the infant. Ideally, contacts would be vaccinated at least 2 weeks before contact with the infant, and pregnant women who had never received Tdap would be vaccinated immediately post-partum. This new strategy required a shift in thinking and a new paradigm for vaccine delivery.

In 2010, the US experienced a resurgence of pertussis. California declared an epidemic and recommended a dose of Tdap for pregnant women. During this time, ACIP recognized the difficulty in widely implementing cocooning programs and considered shifting the timing of the mother's Tdap dose from postpartum to during pregnancy, which would provide earlier direct benefit to mother and potentially indirect protection to the infant, and high levels of transplacental maternal antibodies would likely provide direct immunity to infants.

In 2011, ACIP recommended Tdap during pregnancy for women who previously had not received Tdap, and if not vaccinated during pregnancy, then a woman was recommended Tdap postpartum. In 2012, ACIP expanded the recommendation to every pregnancy, irrespective of the patient's prior history of receiving Tdap. The recommendation for the postpartum dose did not change and, therefore, limited the postpartum dose to women who had not previously received Tdap. For cocooning, guidance on additional Tdap doses for close contacts including the postpartum dose will be forthcoming.

Successful demonstration cocooning programs have been documented. Programs have been primarily hospital-based and targeting the postpartum period. To achieve operational success, common strategies were implemented. For the postpartum dose, standing-orders were in place. For close contacts, hospitals had on-site clinics with convenient hours and offered free Tdap [Yeh S, Mink C, Kim M, Naylor S, Zangwill KM, Allred NJ. Effectiveness of hospital-based postpartum procedures on pertussis vaccination among postpartum women. Am J Obstet Gynecol. 2014 Mar;210(3):237.e1-6; Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013 Jan 11;31(4):618-25; Rosenblum E, McBane S, Wang W, Sawyer M. Protecting newborns by immunizing family members in a hospital-based vaccine clinic: a successful Tdap cocooning program during the 2010 California pertussis epidemic. Public Health Rep. 2014 May;129(3):245-51].

Despite these successes, cocooning has not been implemented at the national level. The challenges programs face are particular to vaccinating close contacts. Logistically, programs are targeting close contacts during a short period of time—the postpartum hospital stay. This may require additional staffing for education and vaccine administration. There is the inability to verify a person's vaccine history, and not all hospitals are set up to treat outpatients and instead may refer family members elsewhere. Financially, there are operational costs to maintaining a program. Programs with free vaccine are challenged to ensure continued funding to offer free vaccine. For programs that do not offer free vaccine, the hospital faces billing and reimbursement challenges. These challenges make it difficult to sustain a program [Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis. 2011 Jan 15;52(2):157-62; Wiley KE, et al. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013 Jan 11;31(4):618-25; Rosenblum E, et al. Protecting newborns by immunizing family members in a hospital-based vaccine clinic: a successful Tdap cocooning program during the 2010 California pertussis epidemic. Public Health Rep. 2014 May;129(3):245-51; Healy CM, et al. Evaluation of the Impact of a Pertussis Cocooning Program on Infant Pertussis Infection. Pediatr Infect Dis J. 2015 Jan; 34 (1):22-26].

In 2012, Tdap coverage was 26% in adults who reported living with an infant aged <1 year, but it is unclear how complete a cocoon is around an infant. Published reports from cocooning programs have reported Tdap uptake highest in postpartum mothers, with limited success in vaccinating fathers or other family members. Tdap uptake has been limited by the knowledge gap about pertussis and the vaccine, household size impacting the ability to vaccinate all

members, and locating where to get vaccinated if no on-site clinic is available [CDC. Urwyler P, Heininger U. Protecting newborns from pertussis - the challenge of complete cocooning. BMC Infect Dis. 2014 Jul 17; 14(1):397; Rosenblum E, et al. Protecting newborns by immunizing family members in a hospital-based vaccine clinic: a successful Tdap cocooning program during the 2010 California pertussis epidemic. Public Health Rep. 2014 May;129(3):245-51; Carrico CA, O'Keefe C. Protecting infants against pertussis: the cocooning strategy in practice. Nurse Pract. 2013 Mar 10;38(3):40-5; Mills B et al. Pharmacist-led Tdap vaccination of close contacts of neonates in a women's hospital. Vaccine. 2014 Jan 16;32(4):521-5; Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis. 2011 Jan 15;52(2):157-62; influenza Vaccination Coverage Among Adults — United States, 2012. *MMWR*. 63(05); 95-102].

For women who receive Tdap postpartum, the limited evidence on the effectiveness of the postpartum dose in preventing infant pertussis is conflicting. A California ecological study noted that pertussis incidence in infants born in hospitals with a postpartum Tdap policy was lower compared to hospitals without a policy, suggesting that vaccinating new mothers may protect infants from pertussis[1]. Another study compared the pre-intervention to the post-intervention period and found no impact of postpartum Tdap on infant disease[2] [[1] Winter K, *et al*. Effectiveness of postpartum Tdap vaccination in California hospitals. CSTE, Portland Oregon. Presented June 2010; [2] Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. Clin Infect Dis. 2012 Jan;54(1):78-84].

The evidence on the effectiveness of cocooning in preventing infant pertussis is unclear and inconclusive. The WG is aware of two US studies that have attempted to evaluate the impact of cocooning: 1) A hospital-based program observed no impact in reduction of infant pertussis, but due to the limitations of the study, results should be interpreted with caution; and 2) An Emerging Infections Program (EIP) study set out to conduct a case-control study to measure effectiveness of cocooning at preventing pertussis among infants <2 months of age. But with limited numbers, the study instead assessed the completeness of cocooning. Among infant cases and controls, a total of 199 cocoons were identified. Among those, only 9 were fully vaccinated cocoons, five of whom for which the mother was the only cocoon member. The Australian cocooning case-control study found moderate reduction in risk of pertussis in infants whose parents were vaccinated at a sufficient time to boost their immune response relative to the infant pertussis incubation period [Healy CM, et al. Evaluation of the Impact of a Pertussis Cocooning Program on Infant Pertussis Infection. Pediatr Infect Dis J. 2015 Jan; 34 (1):22-26.; CDC, unpublished; Quinn HE et al. Parental Tdap boosters and infant pertussis: a case-control study. Pediatrics. 2014 Oct; 134(4):713-20].

Over the past decade, with the changing pertussis epidemiology, a shift in the source of pertussis transmission to infants has been observed. Previously, parents were commonly identified as a source of pertussis, with mothers most often identified. More recently though, siblings have been identified as the most common source. Through enhanced surveillance data over 8 years in the US, among infant pertussis cases, 44% identified a source of infection. Of those, 66% to 85% were classified as family members, with siblings as the most commonly identified family member [Wendelboe AM, et al. Transmission of *Bordetella pertussis* to Young Infants. Pediatr Infect Dis J 2007;26: 293–299; Bisgard KM, et al. Infant pertussis: who was the source? Pediatr Infect Dis J 2004; 23(11):985-989; de Greeff SC, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010 May 15; 50(10):1339-45; Jardine A, et al. Who gives pertussis to infants? Source of infection for laboratory confirmed cases less than 12 months of age during an epidemic, Sydney, 2009.

Commun Dis Intell, 2010. 34(2):116-21; Wiley KE, et al. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013 Jan 11;31(4):618-25; Bertilone C, et al. Finding the 'who' in whooping cough: vaccinated siblings are important pertussis sources in infants 6 months of age and under. Commun Dis Intell Q Rep. 2014 Sep 30;38(3):E195-200].

Since 2011, ACIP has recommended Tdap vaccination for women during pregnancy. Safety data continue to be reassuring for both women and newborns. In 2012, the UK recommended pertussis vaccination for pregnant women. Two recent publications from the same immunization program show agreement of high effectiveness of maternal pertussis vaccination. An observational study used the vaccine screening method. For infants less than 3 months of age at onset of pertussis, vaccine effectiveness was 91% for infants whose mothers were vaccinated at least 28 days before birth. In contrast, effectiveness was 38% for infants whose mothers were vaccinated 0 to 6 days before or 1 to 13 days after birth. A case-control study assessed the effectiveness in infants <2 months of age at onset of pertussis infection. The unadjusted vaccine effectiveness was 91%. When adjusted, the vaccine effectiveness was 93%. The UK was able to achieve high uptake of pertussis vaccine in pregnant women in a short period of time, which allowed for these evaluations [Amirthalingam G, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014 Oct 25;384(9953):1521-8; Dabrera G, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015 Feb 1;60(3):333-7].

Uptake of Tdap among pregnant women has not been as successful in the US. Tdap coverage estimates among pregnant women ranges from 14% to 23% [Kharbanda EO, et al. Receipt of pertussis vaccine during pregnancy across 7 Vaccine Safety Datalink Sites. Prev Med. 2014 Oct;67:316-9; Housey M et al. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid--Michigan, 2011-2013 MMWR Morb Mortal Wkly Rep. 2014 Sep 26;63(38):839-42; CDC. Internet Panel Survey. Women aged 18–49 years pregnant at any time since August of prior year (e.g. 2014 for the April 2015 survey) were recruited in a general population internet panel operated by Survey Sampling International].

After much discussion, the WG has made the following assessments regarding pertussis and vaccinating close contacts of infants with Tdap. The WG recognizes the importance of optimizing strategies for preventing pertussis in infants and that many health-care programs have put a lot of time and effort into cocooning programs. But after 10 years, implementation and sustainability remain a challenge, with barriers preventing close contacts from getting vaccinated. There is a lack of data evaluating the effectiveness and impact of this strategy on preventing infant pertussis, and the evidence is inconclusive that additional doses for close contacts (including the post-partum dose) would be beneficial in prevention of disease and transmission of pertussis to infants. Even if additional Tdap doses are recommended, this would not address the observed shift to siblings as a source of pertussis transmission to infants and puts greater emphasis on the importance of providing newborns with anti-pertussis maternal antibodies. There is an optimal strategy in place, vaccinating women during pregnancy.

At this time, the ACIP Pertussis Vaccines WG concluded that the available evidence does not support changes to the current ACIP Tdap recommendation for close contacts of infants, including the postpartum dose for women. If Tdap vaccines are licensed for additional doses, the ACIP will be asked to reconsider the various policy options. Until then, the focus should be on the current pertussis vaccination program, which is to maintain high levels of DTaP coverage, sustain Tdap coverage in adolescents, improve adult coverage, and vaccinate women during pregnancy to protect infants.

In an effort to improve Tdap coverage in pregnant women, CDC recently launched a new campaign to promote Tdap immunization during pregnancy. After conducting mixed methods formative research, new materials targeting pregnant women and prenatal healthcare professionals were developed in collaboration with co-branding partners AAFP, AAP, ACNM, and ACOG. These are samples of the materials for healthcare professionals:

Dr. Liang pointed out the emphasis on not relying on postpartum immunization in the first fact sheet, and that since reimbursement challenges are a perceived barrier for stocking Tdap, ACOG's reimbursement tools are highlighted an entire sheet was created pertaining to how to make a strong referral.

These are examples of the English and Spanish-language tools for pregnant women. Fortunately, the focus groups revealed that pregnant women are very receptive to getting Tdap once they learn how it can benefit the baby. A strong recommendation from their provider can make all the difference:

Discussion Points

Dr. Temte shared a comment by Dr. Robert Benjamin from Marin County Public Health Department in California so that the workgroup would have this information as they move forward, "Is pertussis elimination and control a national priority? Will the government incentivize the development of a new more immunogenic vaccine?"

Dr. Reingold responded that the WG has attempted to ascertain what type of pertussis vaccines may be under development. The news is not encouraging and better vaccinations are not anticipated in the next few years, so Dr. Benjamin's point is well-taken.

Ms. Pellegrini asked whether there had been any attempt in the sibling studies to ascertain whether siblings were current on their pertussis vaccinations.

Dr. Liang replied that in that assessment, it was not assessed.

Dr. Bennett inquired as to whether there was any sense of the age distribution among the siblings.

Dr. Liang indicated that the siblings in the study ranged from 1 to 19 years of age, with a median age of about 8 years.

Dr. Ault (ACOG) conveyed his and Ms. Hayes' compliments to CDC on the materials for practitioners and pregnant women. He noted that ACOG made its recommendation for vaccination during pregnancy in the Spring of 2013, and he wondered whether there were any data from 2014 and/or 2015 regarding uptake since that recommendation.

Dr. Liang replied that the most recent information available is from the Influenza Internet Panel Survey of Pregnant Women, which was for the 2014-2015 influenza season. Coverage among women during that time period was 23%. The WG is aware that some of the coverage data are for a period of time during the transition from 1 dose to a dose during every pregnancy.

Dr. Plotkin (Vaccine Consultant) said he would like to see more emphasis placed on the timing of vaccination during pregnancy. One of the slides indicated up to 36 weeks. There are data suggesting that the optimal time for vaccination during pregnancy is between 27 and 30 weeks, though these data need to be confirmed. The British data also suggest that vaccinating late in pregnancy does not permit time for transplacental passage of antibodies. Therefore, he suggested placing more emphasis on timing the vaccination earlier in the third trimester rather than at the last moment during pregnancy.

Regarding coverage, Dr. Sawyer (PIDS) emphasized Dr. Liang's point that a strong recommendation from a provider does resonate well with pregnant women. This is illustrated by an effort in the Northern California Kaiser Program that achieved greater than 80% coverage for the last three quarters in their pregnant women.

From a local public health standpoint, Dr. Zahn (NACCHO) the general pushback from local obstetricians has pertained to the vaccination not fitting into their clinical model rather than lack of knowledge. While exhortation and reminding people of the importance of the vaccines are essential, logistically speaking, the reason Kaiser does well with uptake is because there is a place where pregnant women can go to be vaccinated. Pharmacies are not a good option due to insurance issues and barriers. At the local level, he would like to have more clarity on what direction to take beyond posters in terms of where women can be vaccinated consistently.

Dr. Harriman agreed that while a strong recommendation is great, having the vaccine on site is critical so that women can be vaccinated immediately. Even if there are no barriers with insurance at a pharmacy, the issue is getting to a pharmacy. It is known from influenza in many studies that anything that requires harder work to do, life gets in the way and it does not happen. The barriers identified in the ACOG and other studies for prenatal care providers not offering vaccines on-site is either real or perceived financial barriers to setting up a program and/or not being reimbursed adequately. California has a half a million births per year, 50% of which are on Medi-Cal. There are plans to assess uptake within Medi-Cal to determine what is occurring.

Following up on Dr. Harriman's point, Dr. Temte asked whether there were any data assessing family practices that provide obstetrical care versus obstetrical practices per se. His clinic does very well with Tdap and pregnancy, with 80% to 90% of pregnant women receiving the vaccine. However, they do maintain vaccines on-site.

Regarding Dr. Plotkin's comments, Dr. Baker (IDSA) indicated that through CDC funding, one of her colleagues is currently running samples. So, there soon will be precise data with these vaccines of the timing by week in gestation and the amount of antibody transfer. Another study will assess timing at 32 to 34. She works in a hospital in which the pediatric department runs the obstetric service, with a group of academic practitioners and a group of private practitioners who have offices in the same building with the same pharmacy. There is no barrier of access, but there is tremendous disparity even though both groups have been educated. The Baylor Academic group has initiated best practices making this part of the EMR. She agreed with Dr. Harriman that having vaccine available on site is important, but there must also be recommendations by practitioners.

Dr. Riley noted that California is at 89% of pregnant women receiving the vaccine and has been for a long time, so she is disturbed when she sees the numbers at 22%. She asked where they will get the data and whether they will be available moving forward.

Dr. Liang replied that CDC collects data through the Influenza Internet Panel Survey of Pregnant women, which is seasonal for each influenza season, and through the Pregnancy Risk Assessment Monitoring System (PRAMS). There is a PRAMS module in which Tdap coverage among pregnant women is asked about, but that is an optional module. That is, it is not required by all states to choose that set of questions to answer. The last she was aware, at least 13 states have been completing the Tdap coverage module.

Dr. Riley wondered whether a request could be made for mandatory reporting by states of this information.

From a local public health standpoint, Dr. Zahn (NACCHO) reported that far more pertussis is being seen. There have been larger waves of disease, and even when the waves go away, a lot of disease is still being observed. Increasingly, local public health is emphasizing the importance of identifying high risk scenarios (i.e., infants). Nurses in public health always ask him about 28 year old dads with infants who should have received Tdap at 23. While every adult is supposed to be getting Tdap coverage and data suggests that immunity wanes, there is a gap and it is not clear why that 28 person would not be vaccinated. It was not clear to him whether this pertained to cocooning or repeat vaccination. This is a logical quandary that providers ask him about frequently.

Dr. Lett said she did not completely understand how PRAMS is operated and funded, she also made a plea for the Tdap to be part of the core questions. She learned by chance that it was being drafted, and she had to submit a brief and give a presentation to get it included. A board within her state had to approve it, and then she had to provide the funding from her program to keep the question in. Perhaps CDC could make this part of the core funded questions.

Acellular Pertussis Vaccine Effectiveness among Children and Adolescents in the Setting of Pertactin-Deficient B. Pertussis

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Dr. Breakwell emphasized that despite high vaccination coverage, there has been a resurgence of pertussis disease in the US, with notable peaks in 2005, 2010, and 2012. In recent years, reported pertussis has significantly increased and remains elevated compared with the previous decades [2014 data are provisional; SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

There are several factors which could be contributing to the resurgence in pertussis disease. Surveillance bias is one possible explanation. Increased provider and public awareness and improved sensitivity of diagnostic tests, such as PCR, can lead to increased identification and reporting of pertussis disease. Waning of immunity may play a role, as it could increase susceptibility in individuals as time since their last vaccination increases.

Recent investigations have shown that vaccine effectiveness (VE) wanes among children vaccinated solely with acellular vaccines. In a case-control study conducted in California, VE of DTaP among children was 89%. Although VE was excellent within one year of receiving the fifth DTaP dose at 98%, protection waned to 71% by 5 years post-vaccination. This result is consistent with other published studies [Misegades L et al. *JAMA*. 2012;308:2126-32].

Waning of protection was also observed with Tdap. In Washington and Wisconsin, VE of Tdap, estimated by two different methodologies, was 73% to 75% within one year of Tdap vaccination, but waned to 34% by 2 years post-vaccination. A further contributing factor to the resurgence could be genetic changes in the *Bordetella pertussis* bacteria. One such example is the recent emergence of pertactin-deficient pertussis strains. Pertactin may be involved in bacterial adhesion to respiratory tract epithelial cells and in resistance to neutrophil-mediated clearance. It is also a component of all acellular vaccines in use in the US. Pertactin-deficient strains have been identified in Australia, Finland, France, and Japan. In light of this, Dr. Breakwell's branch evaluated the CDC pertussis isolate collection to determine when pertactin-deficient strains emerged in the US and their current national prevalence [[1]Lam C et al. Emerg Infect Dis. 2014; 20:626-33; [2]Barkoff AM et al. Clin Vaccine Immunol. 2012; 19:1703-4; [3]Bouchez V et al. Vaccine. 2009; 27:6034-41; [4]Miyaji Y et al. PLoS One. 2013; 8:e77165; [5]Pawloski LC, et al. Clin. Vaccine Immunol. 2014; 21:119-25].

A pertactin-deficient strain was first identified in 1994, but not again until 2010 when 14% of all isolates lacked pertactin. By 2012, 85% of tested isolates were pertactin-deficient, and currently around 80% of tested isolates are pertactin-deficient. Pertactin-deficiency does not appear to alter clinical symptoms, but may provide a selective advantage as fully vaccinated cases were 4 times more likely to have pertactin-deficient pertussis compared to unvaccinated cases. The impact of pertactin-deficiency on VE is unknown [Pawloski LC et al. Clin. Vaccine Immunol. 2014; 21:119-25; Martin SW et al. Clin Infect Dis. 2015; 60:223-7].

In terms of the first evaluation of pertussis VE among pertactin-deficient pertussis strains, the objectives were to estimate VE and duration of protection of the 5-dose DTaP series among 4- through 10-year olds and Tdap among 11 through 19 years olds; and determine VE for both vaccines among laboratory confirmed pertactin-deficient pertussis strains. Vermont was an ideal place to conduct the evaluation as it had the second highest pertussis incidence rate in 2012. The state laboratory cultures all pertussis specimens it receives, which is a necessary step to determine pertactin status. Based on this, Vermont had a very high proportion of pertactin-deficiency among its tested isolates from 2012 among all ages, at 95%.

Two matched case-control studies were conducted in Vermont. Cases included all probable and confirmed pertussis cases reported during 2011-2013, aged 4 through 10 years for the DTaP evaluation and 11 through 19 years for the Tdap evaluation. Controls were randomly selected from the same age groups from the primary care home of the case in a 3:1 ratio. Cases and controls were matched on primary care home and additionally birth year for the Tdap analysis. Demographics and pertussis vaccination history were collected for all cases and controls from their medical charts. If necessary, vaccination history was further supplemented by parent interviews. Conditional logistic regression was used to calculate odds ratios,

accounting for matching factors. VE was calculated by 1 minus the odds ratio multiplied by 100%.

Cases were classified according to Vermont Department of Health definitions, based on those of the Council of State and Territorial Epidemiologists (CSTE). Persons meeting the clinical case definition were considered probable cases. Confirmed cases were culture positive, or met the clinical case definition and had a positive PCR test, or met the clinical case definition *and* were epi-linked to a lab-confirmed case. Pertactin-deficient strains were pertussis culture positive and confirmed to be pertactin-deficient through molecular testing for specific mutations and ELISA for protein expression [Adapted definitions of Council of State and Territorial Epidemiologists; pertussis case definitions changed in 2014; Pawloski LC et al. Clin. Vaccine Immunol. 2014; 21:119-25; Martin SW et al. Clin Infect Dis. 2015; 60:223-7].

Vaccination status was confirmed by review of medical charts or by parent interviews. For a participant to be considered vaccinated with the 5-dose DTaP series, doses 1-3 were received at less than 1 year of age, dose 4 at 1 to less than 2 years of age, and dose 5 at 4 to less than 7 years of age. For Tdap, a dose was received at or after 11 years of age. Unvaccinated participants were defined as having no pertussis-containing vaccines in their medical chart and had parental confirmation of non-receipt. Overall, 850 cases aged 4 through 19 years were reported to Vermont Department of Health during 2011-2013. Of these, 73% were reported during 2012. Cases came from all 12 public health districts and 91 primary care homes. Data were collected for 820 cases (96% of reported cases) and 30 cases were excluded because their primary care home was based outside of Vermont, they declined to participate, or there was an inability to assign them to a primary care home.

Regarding the 5-dose DTaP series evaluation, data were collected on 382 cases and 1113 controls aged 4 through 10 years. Overall, 31% of cases and 35% of controls were excluded, predominantly for having unverified vaccination history, having received less than 5 DTaP doses, or having 5 DTaP doses off-schedule. Overall, 263 cases and 726 controls were included in the analysis. Of the cases, 71% were confirmed and 29% were probable. Of the confirmed cases, 83% were laboratory-confirmed and 17% epi-linked. Cases and controls had similar demographics, including sex, ethnicity, race, VFC program eligibility, and insurance status. Controls were selected from across the entire age range due to the matching criteria. Cases were more likely to be older and unvaccinated. Of the cases, 93% were vaccinated compared to 99% of controls. VE of the 5-dose DTaP series was estimated at 84%, with 95% confidence intervals ranging between 58% and 94%. The study found that over time, protection waned. During the first year after receipt of the 5th dose of DTaP, VE was 90%. By 5 to 7 years post-vaccination, VE had fallen to 68%, a reduction of 22%. This result is consistent with the other studies mentioned earlier.

Regarding the Tdap evaluation, data were collected on 438 cases and 1256 controls aged 11 through 19 years. Overall, 15% of cases and 13% of controls were excluded, predominantly for having unverified vaccination history or for having received Tdap before they were 11 years old. Overall, 372 cases and 1090 controls were included. Of the cases, 80% were confirmed, of which 90% were lab-confirmed and 10% were epi-linked, and 20% were probable. Cases and controls had similar demographics, including sex, ethnicity, race, insurance status and vaccines for children program eligibility. As a consequence of the matching criteria, similar numbers of cases and controls were included for each age year. Cases were more likely to be unvaccinated, with 70% of cases vaccinated compared to 84% of controls.

To align these findings with current vaccination recommendations, the Tdap VE analysis was restricted to participants who had received only acellular vaccines. Vermont has been a universal purchaser of vaccines since 1993. Following review of vaccine distribution data provided by the Vermont Department of Health, the assumption was made that whole cell vaccines were no longer available after 1997. Therefore, this analysis only included participants born after 1997, which would encompass all participants aged 11 through 12 years and most participants aged 13 through 15 years. Participants who had received only acellular vaccines included 244 cases and 714 controls. Tdap VE was estimated at 70%, with 95% confidence intervals ranging between 54% and 81%. As with the DTaP vaccine series, duration of protection waned with time. During the first year after receipt of Tdap, VE was 76%. By 2 to 4 years post-vaccination, VE had fallen to 56%, a reduction of 20%. This result was consistent with the other studies mentioned earlier.

In terms of pertussis VE among pertactin-deficient pertussis strains, pertactin status can be determined only with culture isolates. Of cases included in the DTaP evaluation, 59% were laboratory-confirmed by PCR or culture, while 75% were laboratory-confirmed for the Tdap evaluation. Of those DTaP cases that were laboratory-confirmed, 61% were pertussis culture positive. Of those, 90% were tested for pertactin deficiency. Of those tested, 98% were pertactin-deficient. Of those Tdap cases that were lab-confirmed, 65% were pertussis culture positive and of these 92% were tested for pertactin deficiency. Of those tested, 95% were pertactin-deficient. Only a limited number of cases from the DTaP VE analysis were pertactin-deficient and met the definition of unvaccinated, preventing the estimation of VE among pertactin-deficient strains. Tdap VE among pertactin-deficient strains was evaluated. Overall, VE was estimated at 51%, with 95% confidence intervals ranging between 5% and 75%. These intervals overlapped with those of previous studies.

In conclusion, initial VE is high but protection wanes over time for both vaccines. These findings are consistent with previous VE estimates. Among pertactin-deficient strains, Tdap VE was found to be lower, but confidence intervals overlapped with the overall VE estimate. This implies that VE among pertactin-deficient pertussis is similar to previous studies, regardless of the prevalence of PRN-deficiency. For example, during the 2010 California outbreak and the 2012 Washington State outbreak, the proportions of pertactin-deficient strains were estimated to be 14% and 76%, respectively. These VE estimates are comparable to those two studies, strongly suggesting that pertactin-deficiency does not impact VE for reported pertussis disease.

Regarding limitations, case-control study designs are commonly susceptible to selection and information bias. To mitigate this, cases and controls were matched on primary care home to ensure exposure to similar circulating pertussis strains and to limit for provider-associated diagnostic and reporting biases. Another limitation in this evaluation was the low proportion of unvaccinated participants with confirmed pertactin-status. Since pertactin confirmation was only completed on 40% of cases, the tested isolates may not be representative of all circulating pertussis strains. In addition, if there is a selective advantage to pertactin-deficiency, more pertactin-expressing strains may be expected among unvaccinated cases. By including these cases in the analysis, vaccine effectiveness may have been over-estimated. The VE estimates also are unlikely to account for mild disease, which may be more prominent among vaccinated individuals and less likely to be reported.

These evaluations suggest that the lack of pertactin among currently circulating strains of pertussis does not substantially impact VE for reported pertussis disease. However, these evaluations did not capture mild or asymptomatic cases and were not able to investigate the impact of pertactin-deficiency on transmission. Given that pertactin-deficiency may potentially provide a selective advantage, further investigations are required to better define the role of pertactin in pathogenesis or transmission.

Herpes Zoster

Introduction

Edward Belongia, MD
Chair, ACIP Herpes Zoster Work Group

Dr. Belongia reminded everyone that in 2006, the FDA licensed a live attenuated zoster vaccine. In 2008, ACIP recommended routine use of this vaccine for all persons over 60 years of age who have no contraindications. In 2011, the FDA approved the vaccine for shingles prevention in people 50 through 59 years of age. However, ACIP did not make any changes to the age recommendations.

Since that time, there have been some new developments. GSK has an investigational adjuvanted vaccine for zoster prevention in healthy adults ≥ 50 years of age. Merck has an investigational vaccine for zoster prevention in immunocompromised individuals. The same GSK vaccine is being evaluated for zoster prevention in immunocompromised individuals.

The WG has been inactive for a period of time. Dr. Belongia recently joined last year when he became a new ACIP member. New members have been added with clinical expertise in immunocompromised patients. The WG history and recommendations have been reviewed, and the WG has heard presentations by manufacturers on herpes zoster (HZ) activities and status of vaccines in development.

During this session, an update was presented on herpes zoster epidemiology and vaccine coverage, and results were presented from a Phase 3 efficacy study of adjuvanted zoster subunit vaccine in adults ≥ 50 years old.

Update on Herpes Zoster Epidemiology and Vaccine Uptake

Rafael Harpaz, MD, MPH
CDC Lead, Zoster Work Group
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Harpaz discussed the clinical manifestations and epidemiology of HZ, the zoster vaccine, recent policy developments, and zoster vaccine uptake. Regarding the clinical picture, HZ manifests as a painful unilateral rash. The rash generally affects 1 to 3 adjacent dermatomes. It develops over approximately 5 to 7 days and generally resolves within approximately 25 days. While the rash can at times cause secondary infections or scarring, and while it can transmit varicella zoster virus (VZV) to susceptible children to cause chickenpox, the primary acute concern regarding HZ is pain, which can at times be

excruciating. About 90% of patients with HZ experience pain, or some kind of distressing sensation. In fact, these symptoms typically precede the rash by 1 to 5 days or more, which can lead to diagnostic dilemmas and work-ups for a cardiac or abdominal etiology, and the uncertainty of it all itself causes patients distress.

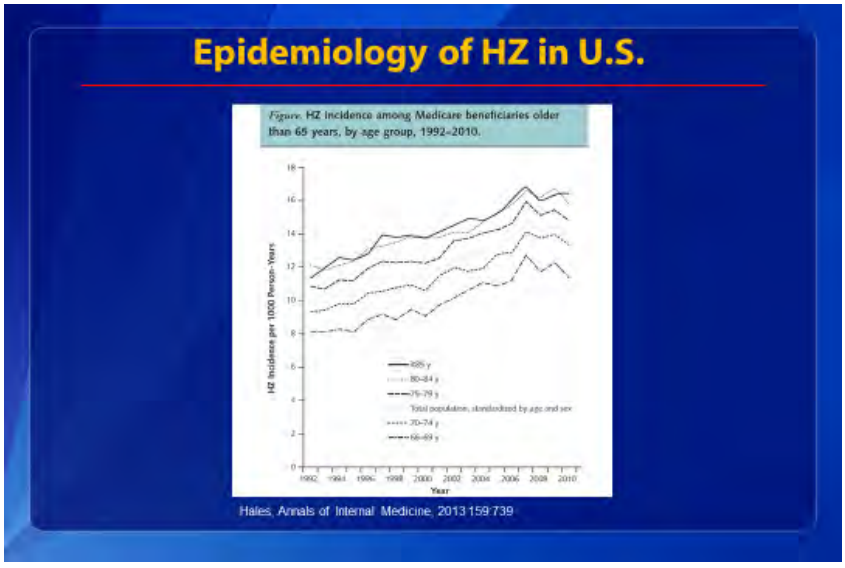
However, the most feared complication of HZ is surely post-herpetic neuralgia (PHN). This is the prolonged, sometimes incapacitating pain that continues after resolution of the rash. While definitions regarding pain duration vary, PHN lasts weeks to months or even years. While prompt use of antivirals may relieve the chronic pain of HZ, treatment of HZ is at best only partially effective at preventing PHN. Furthermore, while there are guidelines for treatment of the PHN itself, these treatments only provide partial and inconsistent benefit. In addition, PHN treatments involve psychotropic medications such as opioids, anti-seizure medications, and tricyclic antidepressants that are often poorly tolerated and cause serious side effects, particularly in the elderly. The underlying pathophysiology of PHN is not known, just as it is not known for HZ. PHN is clearly contingent on HZ, but the extent to which the pathways leading to HZ and to PHN are distinct is unknown. Another common and important complication of HZ is herpes zoster ophthalmicus (HZO), which occurs with involvement of the ophthalmic division of trigeminal nerve. HZO can lead to chronic ocular complications, reduced vision, or even unilateral blindness.

It is difficult to discuss the epidemiology of HZ without first discussing its risk factors. There are two risk factors that are particularly important. The first of these is age. Age is the dominant factor driving incidence and burden of HZ in any population. The rate of HZ really starts to increase at the age of 50 years[1]. Similar data have been reported in virtually every study on HZ ever conducted, regardless of methods. Not only is age the dominant risk factor for HZ, but also it is the primary determinant of the severity of that HZ. The impact of age on PHN is even greater than that for HZ, being approximately 10 times higher in persons >80 compared to those 50 through 59 years of age. In fact, for every 1000 persons with HZ, most severe outcomes increase dramatically with age, especially hospitalization. The oldest old have the least reserve to tolerate PHN, and have the most difficulty tolerating anti-PHN treatments[2] [[1]Marketscan administrative data, Insinga et al., J Gen Intern Med. 2005, 20:748-53; [2]Olmsted County, MN, Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9].

The second key risk factor for HZ is immunosuppression. While this is less common in the population, it remains quite influential due to the magnitude of associated risk. For instance, HZ risk is increased up to 50-fold for hematological malignancies, stem cell transplantation, or HIV infection. In addition, among those experiencing HZ, it is the immunocompromised patients who experience the most serious and even life- or sight-threating complications.

With that background on risk factors, the annual rate of HZ is approximately 4 per 1000 population per year in the US, which translates to approximately 1 million cases annually. The lifetime risk of developing HZ is thus about 30%. While age and immunocompromize explain a large percentage of HZ cases, what distinguishes most of the 30% of persons who develop HZ during life from the 70% who do not is inexplicable. Finally, age-adjusted rates appear to be increasing.

The following graph shows age-stratified Medicare data on HZ incidence among persons 65+ on the Y axis, and calendar time from 1992-2010 on the X axis:



Rates have been increasing substantially over time, for all age groups. This pattern has been also observed in other data from the US, dating as far back as the 1940s. Age-specific increases have been observed in Canada, East Asia, and elsewhere. There is no cohesive explanation for this finding.

Zostavax® was licensed in 2006 based on the Shingles Prevention Study (SPS). The trial involved over 38,000 healthy adults 60 years of age and older who were followed for about 3 years. Subjects were randomized to receive placebo or the attenuated Oka strain VZV found in the varicella vaccine, Varivax®, but at a 14 times or greater titer. Vaccine efficacy was found to be 51% for the HZ outcome, and 67% for the PHN outcome. No SAEs were attributed to the vaccine, though local reactions were common. Based on these results, ACIP recommended routine vaccination of adults of ages 60 and older with a single dose of Zostavax®. Results of the SPS have since been supported by observational studies.

In terms of the results of the SPS focusing on the association of vaccine efficacy as a function of age, Dr. Harpaz highlighted two findings. First, VE for HZ drops steeply with age to just 18% for persons 80 and older. Secondly, not only is VE for PHN generally better, but also it is considerably better preserved as a function of age, with a VE of 39% in persons 80 years of age and older. The vaccine works progressively better at averting the most prolonged episodes of PHN. It is these longest episodes, some that can extend for many years, that are the most critical targets for prevention.

There have been several more recent developments with policy implications in the zoster arena. First, there was a large multinational randomized clinical trial of Zostavax® in persons 50 through 59 years of age. Follow-up lasted just over a year. The vaccine had a VE against HZ of 70%. Based on these results and the associated reassuring safety data, the FDA issued a license for Zostavax® among adults 50 through 59 years of age in 2011. Also, subjects from the original SPS trial of adults then 60 and older were enrolled into a longer follow-up study that extended out approximately 11 years following vaccination. There was no concurrent control group since the controls from SPS were all offered Zostavax® after that study was completed.

Therefore, the long-term follow-up study was unblinded and less-powered than the SPS. Finally, the study relied on historic controls to define protection, but given the rapidly changing incidence in HZ over calendar time discussed earlier, it was hard to draw clear conclusions about waning of protection from this study. In another development, a clinical trial was conducted to compare safety and immunogenicity of a second dose of Zostavax® (booster dose) administered to adults 10 years after a first dose, as compared to immunogenicity in age matched adults receiving a first dose of the vaccine. The immunogenicity outcomes were comparable in 2 study arms, but these immunogenicity outcomes do not adequately predict protection to address many key questions.

With these developments, in October 2013 ACIP reviewed Zostavax® recommendations and left them unchanged; that is, a routine recommendation for 1 dose of Zostavax® in adults aged 60 years and older. This was essentially an example of "programmatic conservatism." On one hand, given uncertainty about waning, a change in recommendation to vaccinate adults at age 50 might leave them unprotected decades later at ages when the burden of PHN would be greatest. But on the other hand, the degree of added protection conferred by a second dose of Zostavax® is unknown, regardless of associated added program costs and complexities. In the absence of adequate evidence on key issues, it was felt that a major change in the Zostavax® program could not be justified, whether to lower the age at vaccination to 50 or to add a second dose recommendation.

Zostavax® uptake among adults 60 years of age and older increased from 1.9% in 2007 to approximately 24% in 2013, though more recent data from Merck on doses delivered suggest a substantial jump by the end of 2014 to 30%. National data suggest that even with modest levels of vaccine uptake, racial and ethnic disparities have been developing. Uptake has been sluggish for a number of reasons. First, there is price. At a catalogue price of approximately $200, HZV is the most expensive adult vaccine on a per-dose basis. Not only does this make the vaccine less cost effective on a societal level, but also it results in high up-front inventory costs for providers, placing them at financial risk. There are also the issues of storage and handling. In the US, HZV must be stored frozen and is the only freezer-requiring vaccine for adults. Many adult providers are not equipped to handle frozen vaccines. Furthermore, in context of inventory price, the chances of freezer failure means that providers feel that their financial risk is even greater. Merck has a program to share part of that risk, but providers may not be aware of that program.

Between 2007-2011, there were repeated supply shortages due to the challenges of manufacturing this very finicky live attenuated vaccine. Merck has done a great job adding manufacturing capacity and the problems now seem resolved. However, during that interval, a lot of time was lost since there was little promotion of the vaccine. Furthermore, it is likely that many physicians and patients became frustrated and lost interest in the vaccine during that time. There are also barriers imposed by the Medicare Part D program. In contrast to commercial health insurers who are obligated by provisions of the affordable care act to cover Zostavax® without any cost sharing by patients, Medicare Part D coverage of Zostavax® paradoxically involves large costs by patients, typically in the range of $100. Some patients need to pay the full vaccine costs up front, with partial reimbursement weeks after filing. The program is also very administratively complex for physicians, though it is fairly seamless for pharmacies. ACIP has heard a number of presentations in the past about the growing role of pharmacies as vaccination sites. This is a recent development affecting all vaccines, but it has had a particular impact on Zostavax® due to pharmacies administering a large percentage of the vaccine. This development does, however, mean that systems for tracking doses of adult vaccine need to be firmly established.

Zostavax® is additionally affected by the same barriers as other adult vaccines and, more generally, adult prevention measures. While this is not the forum to inventory all those barriers, in general, adult providers must address chronic disease management, acute care needs, and administrative burden, leaving them with little time for prevention. Furthermore, adult providers, including public health itself, have less of a "prevention mindset" with seniors. Finally, there is a general fragmentation of health care for seniors, making accountability for prevention challenging.

Results of GSK Phase 3 Study of Investigational Adjuvant-Based Zoster Vaccine

Thomas Heineman, MD, PhD
Director, Clinical Research and Development
GlaxoSmithKline Vaccines

Dr. Heineman indicated that from the beginning, GSK conceived its zoster vaccine program to target two particular high-risk populations, adults 50 years of age and older and immunocompromised adults 18 years of age and older. With that in mind, the herpes zoster adjuvanted subunit vaccine (HZ/su) candidate vaccine was developed. The HZ/su vaccine was specifically designed to elicit strong cellular and humoral immune responses against VZV in these high-risk populations who would be anticipated to be somewhat immunologically resistant to the vaccination. The HZ/su vaccine contains a vaccine antigen, the purpose of which is to target the immune responses of the vaccine to the VZV pathogen. The antigen contained in the vaccine is VZV glycoprotein E (gE), which was selected for a number of reasons, but most particularly because it is expressed abundantly in the virion envelope of the VZV virus and the membranes of VZV-infected cells. Perhaps more importantly, it is a prominent target for VZV-specific cellular and humoral immune responses. In addition to a vaccine that is specific to VZV, a vaccine is needed that stimulates an immune response of sufficient magnitude to enhance the likelihood of protection. With that in mind, the antigen was combined with one of GSK's proprietary adjuvant systems. In this case, the adjuvant system 01_B ($AS01_B$) was selected. The GSK proprietary AS01 adjuvant system is a liposome-based adjuvant that contains 2 immunostimulants: QS-21 and monophsophoryl lipid A (MPL). This adjuvant is designed specifically to enhance both cellular and humoral immune responses to subunit antigens, and was shown in a series of pre-clinical studies in small animals that when gE is combined with this adjuvant, it elicits robust gE-specific $CD4^+$ T-cell and humoral immune responses in mice.

Subsequent to the completion of the pre-clinical program, GSK moved on to Phase 1 and 2 clinical trials, all of which have been published. To highlight a few of the key conclusions from these studies, two doses of HZ/su vaccine administered at 0 and 2 months induced robust gE-specific $CD4^+$ T cell and humoral immune responses in adults 50 years of age and older. These immune responses to the HZ/su vaccine were well-preserved with the subject age, including in adults 70 years of age and older. In older adults, immune responses to the HZ/su vaccine persisted well over time and remained above baseline for 6 years following vaccination. In autologous hematopoietic stem cell transplant (aHCST) recipients and HIV-infected adults, two doses of HZ/su vaccine induced immune responses comparable to those in older adults. Following a cohort of older adults immunized with the HZ/su vaccine over time, at Month 3 (one month after the second dose of vaccine), the cellular immune response peaks at about 19-fold over the baseline level—keeping in mind that all of the subjects are VZV seropositive to begin with. The cellular immune responses decline over time, as would be expected, but begin to

plateau after a couple of years. Thus, at Month 72 or 6 years after the original vaccination, the cellular immune responses remains at approximately 4-fold over the baseline level.

With the Phase 1 and 2 data in hand, GSK moved forward to Phase 3 efficacy studies. The highlight of that component of the program are three pivotal efficacy studies, two of which are being conducted in older adults (ZOE-50 and ZOE-70). The zoster efficacy (ZOE)-50 study is an efficacy study being conducted in adults 50 years of age and above, and ZOE-70 is an efficacy study being conducted in adults 70 years and above. These studies have virtually identical designs except for the age of the subjects enrolled. The third study, 002, is a true efficacy study in aHCST recipients 18 years of age and older. During this session, Dr. Heineman presented the efficacy and safety results of ZOE-50 study. Though not presented, the following supporting studies are part of the HZ/su Development Program:

Study	Population	Objectives	Status
Co-administration studies			
004	≥50 yoa	Influenza vaccine (quadrivalent)	Ongoing
035	≥50 yoa	Pneumococcal vaccine (PPV-23)	Ongoing
042	≥50 yoa	Tdap vaccine	Ongoing
Other older adult studies			
007	≥50 yoa	Lot-lot consistency	Ongoing
026	≥50 yoa	Schedule comparison	Completed
033	≥50 yoa with history of HZ	Safety/immunogenicity	Completed
048	≥65 yoa; prior Zostavax™ recipients	Safety/immunogenicity	Planned
Other studies in immunocompromised populations (≥18 yoa)			
028	≥18 yoa; solid organ malignancy	Safety, immunogenicity	Ongoing
039	≥18 yoa; hematological malignancy	Safety, immunogenicity	Ongoing
041	≥18 yoa; renal transplant	Safety, immunogenicity	Ongoing

The primary objective of the ZOE-50 study was to evaluate the overall vaccine efficacy in reducing HZ risk compared to placebo in adults 50 years of age and older. The secondary analysis objectives were to determine vaccine efficacy in reducing HZ risk compared to placebo in each age stratum (50 through 59, 60 through 69, and 70+ years); and evaluate HZ/su safety and reactogenicity. The secondary protocol-specified objectives to be analyzed upon completion of ZOE-50 and ZOE-70 studies included the following:

- ❑ VE in reducing PHN
- ❑ VE in reducing HZ-associated complications (other than PHN)
- ❑ VE in reducing HZ-related mortality and hospitalizations
- ❑ VE in reducing HZ-associated pain (acute pain and duration of pain)
- ❑ VE in reducing use of pain medications
- ❑ VE in improving QoL
- ❑ Humoral and cellular immunogenicity

Note that these very important and interesting secondary objectives that are part of this study have not yet been analyzed, given that they will be analyzed at the time the ZOE-70 study is completed in order to have maximal power to draw conclusions on the data.

ZOE-50 was a randomized, observer-blind, placebo-controlled study conducted in 18 countries in Asia/Australia, Europe, Latin America, and North America among adults 50 years of age and older stratified by age (50 through 59, 60 through 69 and 70+ years). Exclusion criteria included individuals with a history of HZ, previous vaccination against VZV or HZ, and immunocompromising conditions. The study groups were randomized 1:1 to receive HZ/su vaccine or a saline solution placebo. Two doses of HZ/su vaccine or placebo were injected intramuscularly at 2-month intervals. Contact included visits at Months 0 and 2 for vaccination and at Months 3, 14, 26, and 38. Monthly phone calls were made to subjects for collection of safety data and suspected HZ cases.

Subjects were educated at the beginning of the study and at every opportunity thereafter to recognize a suspected case of HZ, which was defined as “new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis.” Subjects with suspected cases meeting this definition were asked to return to their study site within 48 hours to be evaluated by the study investigators. If the study investigators thought it was clearly not HZ, subjects were sent home. Suspected HZ cases triggered further evaluation that included collection of samples from the rash for PCR evaluation, as well as digital photographs of the rash. The samples were then tested by quantitative PCR (qPCR) and if positive for VZV, the cases were then considered confirmed for HZ. If negative it was considered not zoster. Indeterminate results were sent for final case adjudication by the HZ Adjudication Committee (HZAC).

The results of the study were derived by the analysis of three specific cohorts. The first cohort was the total vaccinated cohort that included 15,411 subjects who received at least 1 dose of vaccine. The mean follow-up time was 3.5 years. This cohort was comprised of 7698 HZ/su vaccine recipients and 7713 placebo recipients, and was the primary cohort for the safety analyses. The second cohort was the modified total vaccinated cohort (mTVC) that included a total of 14,759 subjects, excluding subjects not receiving Dose 2 or who developed HZ within 1 month after Dose 2. The mean follow-up time was 3.2 years. This cohort was comprised of 7344 HZ/su vaccine recipients and 7415 placebo recipients, and was the primary cohort for the efficacy analyses. There was also a diary card cohort with 8926 subjects from the total cohort who were evaluated in more detail for any vaccine reactions. This cohort was comprised of

4460 HZ/su vaccine recipients and 4466 placebo recipients, and was the primary cohort for the reactogenicity analyses.

Regarding the demographics of the subjects, the average age of the enrollees was approximately 62 years. There was a gender distribution of about 61 females and 39 males. Most of the subjects (~70%) were white, with most of the remainder being Asian. Approximately half of the subjects were enrolled in Europe and the remaining subjects were enrolled in either Asia, Australia, Latin America, or North America.

In terms of the results for the mTVC, recall that the primary objective was vaccine efficacy in subjects 50 years of age and older. Vaccine efficacy in this group was 97.2%, with confidence intervals from 93.7% to 99.0%. The efficacy was calculated by comparing the incidence rates in the vaccine and placebo groups. The incidence rate was 9.1 zoster cases per 1000 person years in the placebo group, and 0.3 zoster cases per 1000 person years in the vaccine group. There were 210 HZ cases confirmed in the placebo group and 6 cases confirmed the vaccine group. Efficacy for each of the pre-specified age cohorts (50 through 59, 60 through 69, and 70+ years) was essentially identical to the overall efficacy ranging from 96.5% to almost 98%. There was no indication from the study that efficacy declines with the age of the subject at the time of initial vaccination. For completeness, efficacy in people 60 years of age and above was 97.6% or basically in the same range. As noted earlier, the mean follow-up time was 3.2 years for these analyses. It is important to note the ZOE-50 study remains blinded at the subject level because the study is ongoing. Therefore, to avoid unblinding, vaccine efficacy by year has not been communicated to the study team. However, there is no apparent waning of efficacy by year during years 1 through 4 of follow-up within this study. The analyses were performed by blinded, external statisticians at the group level. Because there are so few breakthrough cases of zoster in the vaccine group, the study team cannot be provided with the year-by-year efficacy numbers without unblinding at the subject level.

Safety analyses were performed for SAEs, potential immune mediated diseases (pIMDs), and deaths. There was no imbalance in these safety endpoints for the vaccine and placebo groups when considered for the duration of the study, or during the 30 days immediately following vaccination. In terms of solicited local symptoms (pain, redness, swelling) reported during the 7 days post-vaccination, approximately 80% of the vaccine group experienced some type of symptom compared to about 12% in the placebo. The most common local adverse event was pain. Of these, about 9.5% of the vaccine group had Grade 3 pain as compared to 0.4% of the placebo group. The median duration of local symptoms overall was 3 days. The median duration of Grade 3 symptoms was 1 day for pain and 2 days for redness and swelling. For solicited general symptoms reported during the 7 days post-vaccination, approximately two-thirds of subjects had some general reaction during the course of the study, with slightly less than one-third in the placebo group having some reaction. The most common reactions in the vaccine group were myalgia, fatigue, and headache. The median duration of general reactions was 2 days for fatigue, gastrointestinal symptoms, headaches and myalgia and 1 day for fever and shivering. The median duration for Grade 3 symptoms, regardless of which category, was 1 day.

To summarize the ZOE-50 results, HZ/su vaccine efficacy was 97.2% for the prevention of HZ in adults 50 years of age and older. HZ/su vaccine efficacy appeared to be age-independent and fully preserved in people 70 years of age and older. HZ/su vaccine efficacy did not wane during the study period. No imbalance was observed in the incidence of safety endpoints (SAEs, potential autoimmune diseases, deaths) between the HZ/su vaccine and placebo groups. Local and systemic reactions to HZ/su vaccine are common in the first 7 days after vaccination, with the large majority being mild to moderate in intensity and short in duration.

Regarding upcoming results and next steps, as mentioned earlier, results are anticipated in the relatively immediate future for the ZOE-70 study and the ZOE-50/ZOE-70 pooled analyses. This will provide additional information of VE against HZ in people 70 years of age and older, as well as data on VE against PHN, HZ-associated pain, et cetera. The efficacy results are also forthcoming from the aHCST study and several ongoing supporting studies (e.g., co-administration studies, safety/immunogenicity in immunocompromised populations, et cetera). In addition to those studies, GSK plans to conduct long-term post-vaccination follow-up with vaccine recipients to assess duration of protection and immune persistence. Other studies will be conducted to follow-up on earlier studies for long-term immunogenicity outcomes. In the near future, the boostability of the vaccine will be assessed at remote times following the initial course. Additional studies also will be conducted to assess the impact of the vaccine-associated reactogenicity on quality of life (QoL), normal daily activities, et cetera.

Discussion Points

Dr. Rubin asked whether AEs were worse following Dose 2 versus Dose 1. Dr. Heineman replied that the incidence of AEs did not change from Dose 2 to Dose 1.

Dr. Romero was struck by the paucity of minority populations in the study, and wondered whether GSK had any plans to try to increase those numbers.

Dr. Heineman responded that the study enrolled approximately 2000 subjects in the US. The proportion of minorities enrolled is dependent largely upon study sites, et cetera. Clearly, they would like to have more minorities in future studies.

Dr. Temte asked whether GSK had a projected timeline for submission to FDA.

Dr. Friedland (GSK) replied that while it was too early to speculate about when the file would be submitted, the study reports will be submitted as soon as they are ready for review.

Dr. Schuchat asked whether Dr. Heineman could comment on plans to assess patients who previously received Zostavax®.

Dr. Heineman responded that GSK does have plans to evaluate the HZ/su vaccine in people who previously received Zostavax®.

Dr. Temte asked whether there were any plans to consider HZ/su vaccine as a pediatric vaccine for primary protection from chicken pox.

Dr. Heineman replied that as of now, GSK has no plans to test HZ/su vaccine as an alternative to the currently available vaccines, but it is an interesting question.

Dr. Kelly Moore (AIM) noted that though the audience may seem somewhat blasé, they were actually thinking, "Wow, that's really exciting!"

Dr. Temte asked Dr. Harpaz whether there was any speculation regarding the increase in zoster rates over time that he discussed.

Dr. Harpaz replied that he has given this a lot of thought and has assessed every possibility that he has ever considered or heard, and has come up with no cohesive explanations. It does not appear to him and others that the increase is associated with the varicella vaccine program as a result of declines in exposure to varicella disease with less external immunological boosting, as has been speculated by some. In particular, the increase in zoster rates started occurring preceding the onset of the varicella vaccine program, and similar increases have been observed in several other countries.

Dr. Reingold pointed out that there is an increasing prevalence of immunocompromising conditions that may increase the risk.

Dr. Harpaz responded that while that was a good point, the studies to which he referred controlled for immunocompromised status and chronic disease status.

Dr. Temte found the results to be very encouraging. He noted that he has seen his practice age for over 25 years, with most of his pediatric population being in their 40s. They routinely see zoster in older patients, and it has incredible effects on QoL. Having a more affordable vaccine would be desirable. In his very ethnically and racially diverse practice, he is always struck that virtually all of his elderly patients know about this vaccine. The problem is the ability to pay. This is a vaccine for which he is certain there are economic disparities in practices.

Regarding the graph Dr. Harpaz showed with the increase in incidence, Dr. Schuchat observed that the last couple of years appeared to show that incidence was flattening or possibly decreasing. She wondered whether that was a significant difference and if thought had been given to this.

Dr. Harpaz replied that this is a fascinating observation that they have been exploring to assess where it is going. The plateauing in the oldest population seems to be continuing. It depends upon the age group.

Day 2: Public Comment

No public comments were offered during this session.

Dr. Temte thanked everyone for all of their service, wished them safe travel home, and concluded the June 2015 meeting with two lines from Shakespeare's last play:

As you from crimes would pardoned be,
Let your indulgence set me free.

Certification

Upon reviewing the foregoing version of the June 24-25, 2015 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster

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TEMTE, Jonathan L., MD, PhD
Professor of Family Medicine
University of Wisconsin School of Medicine and Public Health
Madison, WI
Term: 07/01/2011-06/30/2015

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Acting Executive Secretary, ACIP / CDC
Medical Officer, NCEZID / DHQP / OD
Centers for Disease Control and Prevention
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Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation
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Louisiana State University Health Sciences Center
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Mercy Care Plan
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Director of Children's Outcomes Research Program
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Department of Pediatrics
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Day 2: Dr. Eddy Bresnitz (Merck)

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Centro Nacional Para la Salud de la Infancia Y La Adolescencia / National Center for Child and Adolescent Health
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National Vaccine Advisory Committee (NVAC)
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Associate Director, Emory Vaccine Center
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Pharmaceutical Research and Manufacturers of America (PhRMA)
BRAGA, Damian A.
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Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., MD, MSEd, MPH
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Society for Healthcare Epidemiology of America (SHEA)
WEBER, David, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology
University of North Carolina Schools of Medicine and Public Health
Medical Director, Hospital Epidemiology and Occupational Health, UNC Health Care
University of North Carolina
Chapel Hill, NC

Meningococcal Submissions

amcno

May 18, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Re: ACIP review of serogroup B meningococcal vaccination

Dear Dr. Pickering:

As President of the Academy of Medicine of Cleveland & Northern Ohio (AMCNO), an organization representing more than 5,000 physicians in the Northern Ohio region, I am writing to express our organization's desire for the Advisory Committee on Immunization Practices to approve a comprehensive recommendation for the routine use of MenB vaccines in adolescent and college-age students.

The AMCNO believes that a recommendation for the use of the MenB vaccination, coupled with the existing recommendation for the meningococcal conjugate vaccine, is the best protection our youth have from contracting meningococcal infections. Cleveland and Northern Ohio are home to dozens of college campuses. Voting for the recommendation at ACIP's June 24th meeting allows the opportunity for tens of thousands of students to arrive on our campuses already vaccinated.

ACIP's recommendation will also help ensure that more adolescents are fully vaccinated against meningitis before they reach the age of increased risk, from 16 to 21. Insurers typically will not cover this type of vaccination without a recommendation. Therefore, absent an affirmative action by ACIP, only families able to afford the vaccination by paying out of pocket costs are protected.

The AMCNO physician members support a recommendation of broad and routine use of vaccination against serogroup B meningococcal disease for adolescents and college-age students.

Sincerely,

Matthew E. Levy

Matthew E. Levy, MD

President

6100 Oak Tree Boulevard, Suite 440 • Cleveland, Ohio 44131 • T (216) 520-1000 • F (216) 520-0999 • www.amcno.org

BAYLOR
UNIVERSITY

May 23, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road N.E.
Mailstop A27
Atlanta, GA 30333

Dear Larry:

As President and Chancellor of Baylor University, I write to express my support for ACIP to adopt a broad, routine recommendation of college-age students against serogroup B meningococcal disease.

A number of college campuses have experienced outbreaks of this disease. It is therefore essential that meningitis B vaccines are employed to address this significant health issue. College students are especially at risk due to their age and living arrangements – dorms and apartments which are ideal environments for spreading the disease.

Please help us make these vaccines available to college students as soon as possible.

Thank you for your consideration.

Gratefully,

KEN STARR
PRESIDENT AND CHANCELLOR

One Bear Place #97096 • Waco, Texas 76798-7096 • (254) 710-3555 • FAX: (254) 710-3557 • Ken_Starr@baylor.edu

FINDLAY

May 15, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Re: Meningitis B recommendation

Dear Dr. Pickering:

As president of The University of Findlay, I ask the Centers for Disease Prevention and Control (CDC) to adopt at the June meeting of its Advisory Committee on Immunization Practices (ACIP) a comprehensive recommendation for the immunization of adolescents and college-age students against serogroup B meningococcal disease. Ideally, the recommendation for MenB will mirror the current recommendation for vaccination against other strains of meningococcal meningitis. Since approximately 30 percent of bacterial meningitis cases are MenB, young people are not fully protected against this deadly but preventable disease without this recommendation.

This issue is of particular importance to me in my role as president of a university. As you know, college age students are among those most often stricken by meningitis, and particularly those living in shared facilities such as residence halls. In keeping with our commitment to ensure our campus is a safe environment, we encourage our students to get vaccinated against meningitis. We also work with our local department of health to offer meningitis vaccines to all University of Findlay students and staff. While this is a step in the right direction, it isn't enough.

A recommendation from ACIP that adolescents and young adults receive the MenB vaccine will help keep these students safe as many parents and physicians follow those guidelines as part of children's routine healthcare regimen. In addition, there is a bill pending in the Ohio legislature that would add meningitis vaccination to the state-mandated vaccination requirement for school children, but only as ACIP recommends. Our legislature is depending on the expertise of CDC's infectious disease experts to guide our own public policy at the state level.

We appreciate that ACIP acknowledges that meningitis outbreaks result in preventable deaths and life altering permanent disabilities. We urge that they also keep in mind the far-reaching impact their recommendation will have, particularly on college campuses. As you know, there have been outbreaks of MenB on two college campuses in the recent past. Preventing such an outbreak is not only the responsible thing to do in regard to student health, but it is also far less burdensome to student and local health departments, college administrators, parents, and the students themselves.

1000 North Main St., Findlay, OH 45840-3653 419-434-4510

March 15, 2015. Associated Students of Northern Arizona University #27-4

Associated Students of Northern Arizona University
Meningitis B Vaccine

BY: 2014-2015 ASNAU Senator: Alexandria Buchta

WHEREAS, student government is dedicated to making sure students receive the best education possible while preparing students for a successful future, we recommend the CDC sub-group Advisory Committee on Immunization and Prevention (ACIP) to declare the newly approved Meningitis B vaccine to become a recommended vaccine for incoming college students.

WHEREAS, incoming college freshman are most likely to be infected due to close living quarters and social nature of college students.

WHEREAS, college athletes are frequently together and commonly share items that can serve as a mechanism to transmit disease, promoting a high possibility of becoming infected with this disease. College athletes are frequently together and commonly share items that can serve as a mechanism to transmit disease, promoting a high possibility of becoming infected with this disease.

WHEREAS, there has been an outbreak at the University of Oregon, infecting six individuals within the last four weeks with one death.

WHEREAS, in recent months and years there have been multiple college students who have been infected, attending different universities (San Diego State, Drexel Princeton, and Providence College) across several states, resulting in death and lifelong medical conditions not limited to loss of mental function, hearing and amputation of limbs.

WHEREAS, there are five strains of Meningitis; serogroup B being the most deadly and just recently becoming vaccine preventable.

WHEREAS, Meningitis B resembles the flu but escalates much more quickly.

WHEREAS, Meningitis B can lead to hearing loss, brain and kidney damage, and limb amputations with one in ten cases resulting in death.

WHEREAS, health issuers commonly only cover ACIP recommended immunizations.

WHEREAS, public schools and universities cannot require what is not recommended.

WHEREAS, ACIP met last February but did not make any changes due to a shortened meeting, therefore deferring the topic of Meningitis B recommendations until June 2015.

WHEREAS, government leaders, after the severe outbreak, sent out a Public Safety Announcement strongly urging parents to immunize their children.

WHEREAS, physicians do not stock what is not in demand, making it difficult to access the life-saving vaccine for parents who desire to vaccinate their children.

WHEREAS, ACIP recommendation of this vaccine would result in immunity within a majority of students, allowing incoming students to develop herd immunity and protect their great, young minds and protecting their future from this known killer.

BE IT RESOLVED THAT: We the Undersigned resolve that the needless loss of human potential, life and limb, from Meningitis B can be prevented. Therefore, we urge the recommendation by ACIP that incoming college students receive the Meningitis B vaccine, with such action a priority at their June meeting.

27-4

THE ASNAU SENATE Resolution #27-4

SYRACUSE UNIVERSITY

DIVISION OF STUDENT AFFAIRS
Health Services

May 20, 2015

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas,

An outbreak of meningitis on a college campus can be devastating for the individuals involved and a source of panic and distress for students, parents and administration. Over the past few years we have seen serotype B meningitis outbreaks on both coasts at Princeton, Yale, Providence, Oregon State and UC Davis. According to the National Foundation for Infectious Diseases, meningitis B is now the most common cause of meningococcal disease in adolescents. Likely because an increasing number of students are being vaccinated against other strains of meningitis, but not meningitis B.

This past October the FDA approved the first vaccine for serotype B meningitis. These vaccines were given to students at the affected colleges in mass immunizations after the outbreaks occurred. In order to help lessen the burden and hysteria involved in such mass immunizations and to protect the population of students on campus before an outbreak, I am advocating to the Advisory Committee on Immunization Practices (ACIP) to recommend this vaccination be added to the current immunization schedule.

Currently, New York State Public Health Law requires that all college and university students either receive the Meningococcal Conjugate Vaccine (MCV4) or sign a waiver acknowledging the risks of declining the vaccine. Having the ACIP add the recommendation for meningitis B vaccination to the current recommendation for vaccination with MCV4 will further protect students who are at increased risk on campuses. I appreciate your consideration.

Sincerely,

Spiro Tzetzis, MD
Medical Director, Syracuse University Health Services
stzetzis@syr.edu

111 Waverly Avenue / Syracuse, New York 13244-2320
315-443-9005 / Fax: 315-443-9010

University of Louisiana at Lafayette

OFFICE OF THE PRESIDENT

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Université des Acadiens

May 29, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering:

On behalf of the University of Louisiana at Lafayette, I am writing to urge the ACIP, under the auspices of the Centers for Disease Control, to adopt a broad, routine recommendation for immunization of adolescents and college-age students against serogroup B meningococcal disease.

College campuses across the U.S. have experienced outbreaks of serogroup B meningococcal disease. Meningitis B has been identified by the National Foundation for Infectious Diseases as the most common meningococcal disease in adolescents, which is most likely caused by the increase in vaccinations against other strains of meningitis.

The Food and Drug Administration has approved vaccinations to prevent the disease. Because health providers rely on CDC recommendations with regard to vaccinations, having broad, routine recommendations for the meningitis B vaccine will be a huge step toward ensuring that college students and others who may be at risk are protected against this often fatal disease.

University leaders are particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of fourteen and twenty-four. College students, who fall in this age group, are especially at risk because close living environments increase the opportunity for spreading the disease.

It is important to make meningitis B vaccines available to college students as soon as possible and to as many as possible. Without a broad, routine recommendation, insurers typically will not cover a vaccination. This means that only those who can afford to pay for the vaccine will be protected. This kind of disparity is certainly not consistent with the CDC's mission of protecting public health.

Thank you for considering my request and understanding the concerns of college and university presidents. The fine work that the ACIP and the CDC do to protect the health security of our nation is greatly appreciated.

Sincerely,

E. Joseph Savoie
President

ebl

Office of the Vice President
for Student Affairs
11000 University Parkway
Pensacola, FL 32514-5750

May 22, 2015

Larry K. Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering:

I am a student affairs administrator with nearly 33 years of experience in the field, currently providing oversight to, among other things, student housing, athletics, campus recreation, and student organizations and activities. The health, safety, and success of our students has always been a priority for me and the dedicated professionals with whom I have been fortunate enough to work. I write to urge the Advisory Committee on Immunization Practices (ACIP) to adopt a broad, routine recommendation for immunization of adolescents and college age students against serogroup B meningococcal disease at its June meeting.

According to the National Foundation for Infectious Diseases, meningitis B is now the most common cause of meningococcal disease in adolescents. A number of college campuses have recently experienced outbreaks of serogroup B meningococcal disease, including death of a student athlete at the University of Oregon.

The Food and Drug Administration (FDA) fast-tracked the approval of vaccinations to prevent the disease. CDC recommendations for the meningitis B vaccine will be a huge step toward ensuring that college students and others at risk are protected against this fast-moving and often fatal illness. Those of us work daily with American college and university students are particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of 14 and 24 and college students are especially at risk because residence halls and student apartments are the ideal environments for spreading the disease.

According to the CDC's own data, the fatality rate of meningococcal disease is between 10 and 15 percent, even with swift treatment. In addition, up to 19 percent of survivors suffer permanent complications, which can include injury to the nervous system, deafness, brain damage, and loss of limbs. So not only are the risks significant but the potential outcomes of infection in a college community are dire.

Phone 850.474.2214 Fax 850.474.3131
Web uwf.edu/Student Affairs
An Equal Opportunity/Equal Access Institution

I encourage you and your colleagues to act now to make these vaccines available to our students as soon as possible. Thank you for your time and consideration and for the important work you do.

Sincerely,

James R. Hurd, Ed.D.
Senior Associate Vice President for Student Affairs

TENNESSEE BOARD OF REGENTS

Office of the Chancellor

1415 Murfreesboro Road, Suite 340 | Nashville, TN 37217-2833| Phone 615.366.4403 | Fax 615.366.3922 | www.tbr.edu

May 29, 2015

Dr. Larry K. Pickering
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

On behalf of the Tennessee Board of Regents, I am writing to encourage the Advisory Committee on Immunization Practices to act on the recommendation to broaden routine vaccination of college-age students again Meningococcal Disease Serogroup B.

As Chancellor of one of the nation's largest higher education systems, governing 46 post-secondary educational institutions and providing programs across the state to more than 200,000 students, I am very concerned about meningitis as it is our population that is primarily at risk of the devastating consequences of this terrible disease.

It is my hope that you will give full consideration to a broad recommendation of this important public health issue in an effort to protect our students before they even arrive on the college campus.

Sincerely,

John G. Morgan
Chancellor

JGM:jhc

UNIVERSITY OF Cincinnati

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May 21, 2015

Mr. Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering:

The University of Cincinnati has a strong history with vaccines, as we count among our graduates Dr. Albert Sabin, who developed the oral polio vaccine. We believe proper vaccination is one of the important elements necessary to maintaining the overall health and safety of our students, staff and our campus community.

As President and as the Director of University Health Services, we respectfully ask the Advisory Committee on Immunization Practices (ACIP) to recommend to the Centers for Disease Prevention and Control (CDC) a wide distribution for the vaccine for serogroup B meningococcal disease. In particular, all adolescents and young adults should be provided this vaccine, along with standard meningococcal vaccine for types A, C, Y and W. There should be no question to offering the comprehensive approach to fighting this deadly disease.

With nearly 44,000 students, many of them living in campus residence halls and apartments, our population is particularly vulnerable to meningitis. As you know, young people in such facilities on campus, in military barracks or similar settings, are at greater risk for meningitis.

In recent years, two college campuses with meningitis outbreaks were battling the MenB strain of the disease. Such a situation could be avoided, if all adolescents, young adults and a broad population are encouraged to have a comprehensive meningitis vaccine schedule.

The State of Ohio is considering legislation that would require bacterial meningitis vaccine for school-age children. Should this bill become law, and the full complement of meningitis vaccines be available, it would greatly help improve the health and safety of future students.

Just as Dr. Sabin's polio vaccine dramatically improved health for the wider population, the meningitis B vaccine will represent a tremendous advancement in our ability to fight infectious disease. Please encourage the ACIP committee to adopt a wide recommendation for this important vaccine.

Thank you for all that you do to address public health.

Sincerely,

Santa J. Ono, PhD
President
University of Cincinnati

Philip M. Diller
Interim Director, University Health Services
The Fred Lazarus, Jr., Professor and Chair
Department of Family and Community Medicine

UNLV | Office of THE PRESIDENT

UNIVERSITY OF NEVADA, LAS VEGAS

May 26, 2015

Stephanie Thomas, Administrator
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Ms. Thomas,

As president of the University of Nevada, Las Vegas, I write to urge the Advisory Committee on Immunization Practices (ACIP) under the auspices of the Centers for Disease Control (CDC) to adopt at its June 2015 meeting a broad, routine recommendation for immunization of adolescents and college-age students against serogroup B meningococcal disease.

As you know, a number of college campuses across the country have recently experienced outbreaks of serogroup B meningococcal disease. According to the National Foundation for Infectious Diseases, meningitis B is now the most common cause of meningococcal disease in adolescents. This is most likely because an increasing number of students are being vaccinated against other strains of meningitis, but not meningitis B.

Fortunately, the Food and Drug Administration (FDA) recognized the threat of meningitis B and fast-tracked the approval of vaccinations to prevent the disease. CDC recommendations for the meningitis B vaccine will be a huge step toward ensuring that college students and others at risk are protected against this fast-moving and often fatal illness. Health providers rely on CDC recommendations to determine which patients need which vaccination.

Vaccinations against diseases like bacterial meningitis are one of the most significant public health achievements of our time. When it comes to this and other infectious diseases, no treatment is more effective than vaccination.

As a university leader, I am particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of fourteen and twenty-four, and college students are especially at risk because residence halls and apartments are the ideal environments for spreading the disease.

Moreover, without a broad, routine recommendation, insurers typically will not cover a vaccination. This means only those who can afford to pay out of pocket for the vaccine will be protected. Certainly, this kind of disparity is not consistent with the CDC's mission of protecting the public health. I urge you therefore, to make these vaccines available to all our students as soon as possible, to avoid a tragedy that we could have averted.

Thank you for considering this request, and for all that you, in the ACIP, and the CDC do to increase the health security of our nation.

Sincerely,

Len Jessup
President

Box 451001 • 4505 S. Maryland Parkway • Las Vegas, NV 89154-1001 • Tel: 702-895-3201 • Fax: 702-895-1088

UTAH VALLEY UNIVERSITY

Student Health Services

June 11, 2015

Ms. Stephanie Thomas and the Advisory Committee on Immunization Practices,

We feel that it is appropriate to give a cautious recommendation to the ACIP to recommend the immunization of adolescents and college age students against serogroup B meningococcal. As we know menigitieous causes significant morbidity and mortality worldwide and even more so in college age student due to their close proximity with each other, especially in living quarters. Utah department of health has also reported an increase in group B meningitis in Utah[1].

However, we feel that caution must be taken and the roll out of this vaccine needs to be in a well-planned manner. The vaccines for Group B Meningitis is new, not even a year old in the US. We spoke with the Utah County immunization clinic and they do not carry the vaccine but it is available by special order. They estimate that it would cost $200 per dose and 2-3 doses are required. We am also cautious because the efficacy, and duration of protection is not yet fully understood. The expert state that they need a population-based study to be done and to do that study the vaccine would need to be widely used, such as after routine immunizations. Studies thus far also suggest that if the vaccine is widely used that it would produce herd immunity that would help protect those students who have not received the vaccine, due to cost or personal preference. Obviously cost would be a great concern to the cash strapped college student. We agree that this is an appropriate preventive measure that insurances should cover.

The roll out of the vaccine needs to be done properly because for the general student population and the campus as a whole to benefit the majority of people need to be vaccinated, not once but receive 2-3 doses. The students will need to be well educated about the benefits and risks to the vaccine and how important it is that they return for a 2nd or 3rd dose. Limited studies have shown that people that only get one dose have a 7376% increase in bactericidal tiers against Group B Meningitis 6 months after the injection. While 99-100% those who receive 2-3 doses had increased bactericidal tiers against Group B Meningitis 6 months after the injection. Proper follow-up is going to be very important.

We have partnered in the past with the Utah County Health Department to provide immunization on campus to students. We also have a presence at the county immunization coalition. The county is really best suited to undertake a mass vaccination effort for the student body. Especially since they are able to bill insurances and we are not. We would participate in this effort by helping to educating the student body, and facilitate a vaccine fair on campus.

Overall, we feel that UVU is at low risk from an immediate Group B meningitis outbreak as we do not have traditional student dorms but have more apartment style

800 West University Parkway MS200 Orem, UT 84058 Phone 801-863-8876 • Fax 801-863-7056

Student Health Services

living for the student. Also UVU Student Health Services and UVU Student Wellness does a fantastic job in promoting prevention and healthy living. Preventing the danger of a future outbreak at UVU is important and that is why we agree with the recommendations to include this in routine immunization. To fully benefit from this insurance companies need to cover the vaccine and the roll out needs to be done in a well-planned out manner.

Thank you for your consideration,

Esme Anderson, APRN, FNP
Director of Medical Services
Nurse Practitioner
Derrick Pickering, APRN, FNP
Nurse Practitioner

http://health.utah.gov/epi/diseases/meningococcal_disease/plan.pdf

1. http://www.uptodate.com.xlib1.intermountain.net/contents/meningococcalvaccines?source=search_result&search=serogroup+B+Meningococcal+Vaccine&selected Title=5~6#H28

800 West University Parkway MS200 Orem, UT 84058 Phone 801-863-8876 • Fax 801-863-7056

THE TEXAS STATE UNIVERSITY SYSTEM

June 3, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E. Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

As chancellor of the Texas State University System, I encourage the Advisory Committee on Immunization Practices (ACIP), under the auspices of the Centers for Disease Control (CDC), to adopt at its June 2015 meeting a broad, routine recommendation for immunization of adolescents and college-age students against serogroup B meningococcal disease.

As the chief executive officer of a statewide system of universities and colleges of over 80,000 students on 14 campuses spanning the breadth of our state, I am concerned because, according to the CDC, the fatality rate of meningococcal disease is between 10 and 15 percent (even with swift treatment) and because, I am informed, a number of college campuses have recently experienced outbreaks of serogroup B meningococcal disease, including the death of a student athlete at the University of Oregon. I am further informed that one in five of all meningococcal infections occur in young adults between the ages of 14 and 24 and that college students are especially at risk because dorms and apartments are ideal environments for spreading the disease.

I am advised that, without a broad, routine recommendation, insurers will not typically cover a vaccination, meaning that only those who can afford to pay out of pocket for the vaccine will be protected. Many Texas State University System students will not be able to afford the vaccine.

We ask that ACIP do all within its power to make these vaccines available to all students as soon as possible, for these young people are the future of this nation.

Sincerely,

Brian McCall, Ph.D.
Chancellor

THOMAS J. RUSK BUILDING
208 E. 10th Street, Suite 600 • Austin, TX 78701-2407 • (512) 463-1808 • fax: n/a

Larry K. Pickering, M.D.
June 3, 2015
Page 2

cc. President, Lamar University
President, Sam Houston State University
President, Sul Ross State University
President, Texas State University
President, Lamar Institute of Technology
President, Lamar State College-Orange
President, Lamar State College-Port Arthur

WESTERN MICHIGAN UNIVERSITY
Office of the President

June 9, 2014

Larry K. Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

I am writing on behalf of Western Michigan University and the WMU Homer Stryker M.D. School of Medicine. We support efforts to broaden indications for use of Meningococcal vaccines as a routine vaccination for college age students. As you know, this issue is on our radar with the college age population suffering from recent deaths contributed to type B breakouts.

We believe a broad, routine recommendation for use of the Meningitis B vaccine would save lives. Timely attention to this matter will help promote health and prevent avoidable disease prior to the start of the September, 2015 academic term.

Thank you for your consideration. Your effort with this important matter is appreciated.

Respectfully,

John M. Dunn
President

1903 W. Michigan Ave., Kalamazoo, MI 49008-5202
PHONE: (269) 387-2351 FAX: (269) 387-2355
WEBSITE: www.wmich.edu/president
CAMPUS SITE: 3065 Seibert Administration Building

UNIVERSITY OF OREGON

June 15, 2015

Advisory Committee on Immunization Practices (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329

Dear Chair Temte and ACIP Members,

The University of Oregon urges the Advisory Committee on Immunization Practices (ACIP) to adopt a broad, routine recommendation for immunization of adolescents and college age students against the serogroup B meningococcal disease at your June meeting. A number of college campuses have recently experienced outbreaks of meningitis B, including the University of Oregon, University of California, Santa Barbara, and Princeton University. During the 2015 outbreak at the University of Oregon, six students and one parent became ill with meningococcal disease and, tragically, one of our students died. These instances make clear the urgency of a timely decision to ensure the immunization of a broader population to prevent future tragedy.

As you know, an increasing number of students are routinely vaccinated against other strains of meningitis, but not meningitis B. According to the National Foundation for Infectious Diseases, this increasing frequency of vaccination against other strains has now made meningitis B the most common cause of meningococcal disease in adolescents. Fortunately, the Food and Drug Administration (FDA) gave its approval of vaccinations to prevent the disease. At its February meeting, ACIP recommended the use of vaccine for at-risk populations in response to outbreaks. ACIP approval for broad, routine immunization would be a step toward preventing another outbreak and ensuring that college students, young people, and others at risk are protected against this fast-moving and often fatal illness.

Meningococcal disease is devastating. As university leaders, we are particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of 14 and 24, and college students are especially at risk because residence halls, fraternities and sororities, and apartments are the ideal environments for spreading the disease.

OFFICE OF THE PRESIDENT
1226 University of Oregon, Eugene OR 97403-1226 T (541) 346-3036 F (541) 346-5017 www.uoregon.edu

Further, a broad, routine recommendation for immunization of adolescents and college age students against the serogroup B meningococcal disease will ensure that insurers will cover the vaccination. This will assist in assuring that all students who need the vaccine are able to get it.

Simply put, we urge your timely review and approval of a broad, routine recommendation for immunization against meningitis B to keep *all* our students safe and avoid another tragic outbreak.

Sincerely,

Scott Coltrane
Interim President
University of Oregon

Robin Holmes
Vice President
Division of Student Life
University of Oregon

Student Government
UNIVERSITY OF COLORADO **BOULDER**

University of Colorado Student Government
Legislative Council

May 18, 2015

83 LCR 01: Meningitis B Vaccination

Sponsored by:
Eileen Sherman — Director of City and Neighborhood Relations
Joseph Soto — President of External Affairs

Authored by:
Boneth Ahaneku — President of Internal Affairs

A Resolution in Support of the Advisory Committee on Immunization Practices (ACIP) Requiring Meningitis B Vaccinations for Incoming Students on College Campuses

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Resolution History

Meningitis is a rare infection of the area known as the meninges which cover the brain and spinal cord. Meningitis symptoms can easily be mistaken for the flu, but are serious and can lead to death and lifelong medical conditions not limited to loss of mental function, hearing and amputation of limb. This dangerous infection is especially prevalent on college campuses due to the close quarters and age of the students, as well as the social nature of campus. Currently, Colorado requires students attending its public universities to be educated and receive the meningitis vaccine. Unfortunately, this vaccine required by the state only covers four of the five strains of Meningitis. The strain not covered is Meningitis B which is the most deadly and requires a separate vaccine that only recently became available. At this time, the Meningitis B vaccination is not required. Meningitis B has been infecting students on college campuses due to the lack of vaccination and awareness of the disease and vaccine. University leaders across the nation are especially concerned because of recent deaths across the nation including, but not limited to, University of Oregon, Princeton University, San Diego State University, Drexel University, and Providence College. They are also concerned about Meningitis B because one-fifth of all infections occur in young adults between 14-24, and because the close living quarters of their fellow college students creates ideal environments for the disease.

American Association of Colleges of Pharmacy
Discover • Learn • Care: Improve Health

Dr. Larry Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27

		Vote Count
5/21/2015	Approved on First Reading	Acclamation
6/4/2015	Approved on Second Reading	Acclamation

Nicholas Trevino
Legislative Council President

John Urquin
President of Student Affairs

Boneth Ahaneku
President of Internal Affairs

Joseph Soto
President of External Affairs

Colorado State University

Office of the
Provost and Executive Vice President
108 Administration Building
1001 Campus Delivery
Fort Collins, Colorado 80523-1001
(970) 491-6614
www.colostate.edu

June 9, 2015

Stephanie Thomas
Advisory Committee on Immunization Practices
1600 Clifton Road, NE
Atlanta, GA 30333

Dear Ms. Thomas:

On behalf of Colorado State University and our students, I respectfully urge the Advisory Committee on Immunization Practices (ACIP) to adopt a broad, routine recommendation for immunization against meningitis serogroup B for adolescents and college age students.

According to the National Foundation for Infectious Disease, meningitis B is now the most common cause of meningococcal disease in adolescents, mostly due to the successful implementation of a recommendation for routine immunization of college students with the quadrivalent meningococcal vaccine, which covers four other serotypes. Nearly 20 percent of meningococcal infections occur in young adults between the ages of 14 and 24. Further, college students are at higher risk of infection because of shared living arrangements and the fact that bacterial meningitis is often initially misdiagnosed leading to a high rate of death or disability. Regrettably, the fatality rate for such infections is as high as 15%.

In recent years, many university campuses have experienced outbreaks of meningitis. In 2010, we experienced an outbreak of meningococcal disease due to serotype C in northern Colorado, with several deaths, leading to a mass vaccination clinic on the CSU campus where approximately 13,000 people were immunized with the quadrivalent vaccine. A broad immunization recommendation from ACIP will lead to many additional students being vaccinated prior to an outbreak, helping campus leaders across country keep their student population safe. Wider use of these vaccinations will not only prevent many cases of infection but also help limit the extent of outbreaks should they occur.

As you know, preventative care is more effective than responding to an outbreak, and will prevent unnecessary disability and deaths. I urge an ACIP recommendation of vaccination against meningitis serogroup B to help university leaders protect our students. I would like to thank ACIP for considering this important matter and for the important work you do to protect and improve health.

Sincerely,

Rick Miranda
Provost and Executive Vice President

Student Government
UNIVERSITY OF COLORADO **BOULDER**

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E.
Atlanta, GA 30333
ACIP@CDC.GOV

Dear Ms. Thomas:

We, the University of Colorado Boulder Student Government, strive to promote a campus atmosphere that allows students to thrive & succeed. This includes a focus on protecting the health and well being of our students. Within the Student Government, we have made it a priority to keep our fellow students well informed about health risks, including from infectious diseases such as meningitis. We applaud both the University and our state government for making meningitis vaccines a priority for incoming students. Since we have become aware of the threat of meningitis B, we put forward the attached resolution to encourage ACIP to recommend that college students vaccine for college students as a positive step to maintaining our desired healthy student body.

We feel strongly about this recommendation and attached a copy of the University of Colorado Boulder Student Government Resolution that was passed *unanimously* on June 4th, 2015.

We hope that as you make your decisions on meningitis B that you keep our students, the students of the University of Colorado, and the students around our great nation in mind.

Thank you for your service and commitment to keeping our nation healthy and for considering our resolution.

Sincerely yours,

Boneth Ahaneku
President of Internal Affairs &
Neuroscience and Molecular, Cellular, Developmental Biology Major at
University of Colorado Boulder

Sierra's Race Against Meningitis

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas & ACIP Members:

We lost our daughter Sierra, April 10, 2007, to Meningococcal Meningitis, a vaccine preventable disease. Sierra was 2 months away from turning 21 years old, working her way through college to fulfill her dream of becoming an elementary school teacher. She was everything good in this world, never afraid to share her outlook on life with anyone and everyone. Easter morning 2007, Sierra was her happy, healthy, loveable self, by evening she become sick with classic flu-like symptoms that always disguise the killer bacteria working to destroy your body. Within 24 hours she was in the emergency room on a ventilator. The following morning, on our beautiful Sierra succumbed to the devastating bacteria that invaded her body, Meningococcal Meningitis. Our family was not aware of this fatal disease, or of the vaccine that could have prevented it, until it was to late. Our lives from that day forward would never be the same, we were now missing a huge piece of our life, a piece that could never be replaced, but her spirit lives on in us and guides us as we do everything we can to help others.

Unfortunately we can't change what happened to Sierra, or the many other victims of this devastating disease, but we can prevent this horrible tragedy from happening to anyone else. This is our goal.

Sierra's Race Against Meningitis came to be as our effort to get the word out about this horrible disease. 100% of our proceeds/donations go to free vaccination clinics and awareness of the disease. We have provided over 4300 free vaccinations in the last 8 years. We miss Sierra more then words can express, we find comfort in knowing we are doing our best to make sure others don't have to go through what we have and continue to go through.

We strongly believe that the meningitis B vaccine should be recommended the way the other meningitis vaccines are because we do not want to wait for an outbreak to occur and risk any lives. We respectfully ask ACIP members vote to recommend meningitis B vaccines be added the regular vaccination schedule.

Thank you for considering our requests and for the work ACIP does to keep our nation healthy.

Sincerely,
Lisa & Jon Krizman
Sierra's Race Against Meningitis
970-310-9103
www.SierrasRaceAgainstMeningitis.com

SACRAMENTO LGBT COMMUNITY CENTER
1927 L Street, Sacramento, CA 95811 • 916.442.0185 • Saccenter.org

June 2, 2015

Ms. Stephanie Thomas
Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention 1600
Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas:

I urge the Advisory Committee on Immunization Practices to consider recommending broader meningitis vaccination for youth and LGBT populations, especially those living with HIV. This issue rose to my level of consciousness as several recent unexplained outbreaks rocked California's gay communities, one of which resulted in the death of a personal acquaintance.
Similar meningitis B outbreaks on college campuses across California, including locally at UC Davis have been in the news. Those who are HIV positive seem to be at even greater risk for contracting the disease, accounting for more than half of the infections.

The the danger to students living and socializing in close quarters and to younger members of the LGBT community, specifically those living with HIV, is both potentially grave and totally preventable. I understand that awareness campaigns and efforts to vaccinate are currently recommended at the hyper local level when there is an identified outbreak. Unfortunately, once an outbreak occurs it's too late for those who are already infected and unknowingly putting their friends, neighbors, and sexual partners at risk.

At the Sacramento LGBT Community Center we provide support to hundreds of LGBT youth ages 13-25 every month, many of whom are homeless or experiencing other conditions that put them at higher risk for communicable and sexually transmitted diseases. Too often they do not know they are infected or wait too long to seek treatment because they lack health insurance and continue to spread infections. We work to educate them on their risks, provide HIV testing, and connect them with supportive health resources and insurance, but can only do so much with the tools available. While we may not yet have a vaccine to prevent the spread of HIV, the FDA has approved vaccines to prevent meningitis. I urge you to make them more available by recommending broader meningitis B vaccination for higher risk populations including young people living and socializing in close quarters as well as LGBT and HIV positive individuals before additional outbreaks occur and lives are lost.

Sincerely,

David Heitstuman
Board President

ACIP

Advisory Committee on Immunization Practices
Office of Infectious Diseases
Centers for Disease Control and Prevention

Public Comment Sign-In Sheet

(Please limit your comments to three minutes)

June 2015

Name: Steven Black, MD

Organization: Division of Infectious Diseases and Center for Global Health, Cincinnati Children's Hospital Cincinnati, Ohio

Mailing Address: 3333 Burnett Avenue
City: Cincinnati State: Ohio Zip: 45229
Phone Number: 510-219-7372
E-mail Address: Stevblack@gmail.com

ACIP Topic: Meningococcal Vaccination June 24, 2015

Comments: I wish to present my perspective on the burden of meningococcal disease, the impact of disease on individuals who become ill and to support a universal adolescent recommendation for Meningococcal B vaccination. In my opinion, decision criteria for vaccination should be multifactorial and take other factors than cost-effectiveness into account. To not do so makes vaccination a cost management tool rather than a public health tool. Other factors that have been proposed include the morbidity and mortality of the disease, the potential to cause outbreaks, and impact on future productivity. Meningococcal disease has both a high case mortality and morbidity rate and outbreaks induce fear in the population. Furthermore, the disease has a great impact on families and friends of people who contract the disease. I wish to share one such story. After many decades of vaccine development, we now have the ability to control this disease. While it is relatively rare, it still causes more than 500 cases 50 deaths per year and leaves half of cases with life long disability. As care givers and physicians, we should seize the opportunity to address this disease burden.

(Provide comment form to ACIP Staff)

THE UNIVERSITY OF TEXAS AT AUSTIN

William Powers, Jr., President
University Distinguished Teaching Professor
Hines H. Baker and Thelma Kelley Baker Chair in Law
Main Building 400 · PO Box T · Austin, Texas 78713-8920

Direct Number (512) [illegible] 1232
Facsimile Number (512) [illegible]
president@po.utexas.edu

May 6, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Larry:

As president of The University of Texas at Austin, I write to urge the Advisory Committee on Immunization Practices (ACIP) under the auspices of the Centers for Disease Control (CDC) to adopt at its June 2015 meeting a broad, routine recommendation for immunization of adolescents and college-age students against serogroup B meningococcal disease.

As you know, a number of college campuses across the country have recently experienced outbreaks of serogroup B meningococcal disease. According to the National Foundation for Infectious Diseases, meningitis B is now the most common cause of meningococcal disease in adolescents. This is most likely because an increasing number of students are being vaccinated against other strains of meningitis, but not meningitis B.

Fortunately, the Food and Drug Administration (FDA) recognized the threat of meningitis B and fast-tracked the approval of vaccinations to prevent the disease. CDC recommendations for the meningitis B vaccine will be a huge step toward ensuring that college students and others at risk are protected against this fast-moving and often fatal illness. Health providers rely on CDC recommendations to determine which patients need which vaccination.

Vaccinations against diseases like bacterial meningitis are one of the most significant public health achievements of our time. When it comes to this and other infectious diseases, no treatment is more effective than vaccination.

As a university leader, I am particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of fourteen and twenty-four, and college students are especially at risk because dorms and apartments are the ideal environments for spreading the disease.

Larry K. Pickering, M.D.
May 5, 2015
Page 3

Moreover, without a broad, routine recommendation, insurers typically will not cover a vaccination, meaning only those who can afford to pay out of pocket for the vaccine will be protected. Surely inculcating this kind of disparity is not consistent with the CDC's mission of protecting the public health.

We must make these vaccines available to all our students as soon as possible, before another tragedy strikes that we could have averted.

Thank you for considering this request, and for all that you, the ACIP, and the CDC do to increase the health security of our nation.

Sincerely,

William Powers, Jr.
President

WP/mwd

THE UNIVERSITY OF IOWA

Student Health & Wellness
4189 Westlawn
Iowa City, Iowa 52242-1100
319-335-8392 *Fax* 319-335-8249
http://studenthealth.uiowa.edu

May 27, 2015

Dr. Larry Pickering, the Executive Secretary ACIP
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering:

As Director of Student Health & Wellness at the University of Iowa, it is my responsibility to ensure my campuses are as safe and healthy as possible. There is no doubt that even one case of meninigitis can cause great harm to any college campus, especially one as big as The University of Iowa. My understanding is that you and ACIP can help protect The University of Iowa and other universitites and colleges.

By adopting a broad reccomendation for routine vaccinations against serogroup B meningitis at your meeting in June, it is my hope current and future Hawkeyes, as well as all other students attending college, will be protected from this form of meningicocal diseases. As we have seen during the past few years, college campuses have sadly been impacted by the deaths of students suffering from serogroup B meningitis.

College campuses, like high schools, keep students in close proximity to each other, raising the likihood that a single case of meningitis will spread. A broad reccomendation which includes college age students will help stop meningitis from spreading.

It is my hope ACIP will vote and make the appropriate reccomendations for these new vaccines to protect students from serogroup B meningicocal disease.

Thank you for your time and consideration of this matter.

Sincerely,

James P. Kellogg, Jr.
Director, Student Health & Wellness
The University of Iowa
Ph: 319-384-1135
james-kellogg@uiowa.edu

UNIVERSITY OF HOUSTON SYSTEM
UNIVERSITY OF HOUSTON

RENU KHATOR
Chancellor and President

June 11, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

The University of Houston System encompasses three universities and teaching centers in the Greater Houston metropolitan area, and one university in Victoria, Texas. As system chancellor, I am responsible for the education and well-being of more than 68,000 students.

I write today out of concern that, according to the CDC, the fatality rate of meningococcal disease is an alarming 10 to 15 percent – even when the patient is treated swiftly. I know that a number of universities have recently experienced outbreaks of serogroup B meningococcal disease, putting thousands of students at risk.

Of particular concern is the fact that one in five of all meningococcal infections occur in young adults between the ages of 14 and 24. College students are part of this age group, and they are especially at greater risk because on- and off-campus student dorms and apartments are ideal environments for the spreading of the disease. At the flagship University of Houston alone, close to 8,000 students live on campus and nearby housing – we have the second highest residential student population in Texas.

I encourage the Advisory Committee on Immunization Practices (ACIP), under the auspices of the Centers for Disease Control, to adopt at its June 2015 meeting a broad, routine recommendation for the immunization of adolescents and college-age students against serogroup B meningococcal disease. I am advised that, without this recommendation, insurers will not typically cover a vaccination, with the result that only those who can afford to pay will be protected. If that is the case, many of our students who come from first-in-college families and difficult financial situations will not be able to receive the vaccine, putting them and all those around them in danger.

212 E Cullen Building • Houston, Texas 77204-2018 • 713.743.8820 • Fax: 713.743.8837

We respectfully ask that ACIP act quickly with all means within its power to make the vaccine available to all students as soon as possible. I thank you, on behalf of our students, for your consideration.

With warm regards,

Renu Khator

Renu Khator

cc: William Staples, President, UH-Clear Lake
William Flores, President, UH-Downtown
R. Victor Morgan, President, UH-Victoria
Jason Smith, Vice Chancellor for Governmental and Community Relations, UH System

National Vaccine Information Center

www.NVIC.org

June 19, 2015

Dr. Jonathan Temte, Chair
The Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333
Email

Re: NVIC Public Comment on ACIP Meningococcal Vaccine Sero Type B Recommendations

Dear Dr. Temte,

Attached is our public comment for the upcoming ACIP meeting on June 24th. I would like to express my personal thanks for your efforts to make public comment available to those who listen to the meeting via webinar. While we are disappointed that public comment will not be available to those listening online, we are sincerely grateful for your offer to read our comment to the committee. It seems that most comments given during ACIP meetings are about three to five minutes in length. The attached comment is about 3 minutes in length.

We are also appreciative that it would be a daunting task to make public comment available under the current format. It has been my experience that many who listen on the phone and in the room do not offer public comment. However, it is important to create equity for the public to comment without having to journey to Atlanta. Perhaps it would be possible to split the public comment time equally between those online and those present and require registration on a first come first serve basis with a time limit for individual comments?

For example, if the public comment session is 30 minutes, 15 minutes could be allotted to those online and those in the room with five people on the phone being able to give comment and five in the room giving comment, with each getting three minutes for comment.

Again, we appreciate your efforts to make ACIP meetings more accessible to the public, as well as your service to the public as you step down from the committee.

Please don't hesitate to contact me with any concerns or questions regarding our comment at tkw.nvic@gmail.com.

Best regards,

Theresa Wrangham
Executive Director

21525 Ridgetop Circle, Suite 100 Sterling, VA 20166 • Phone 703.938.0342 • Fax 571.313.1268

Advisory Committee for Immunization Practices – June 24, 2015 National Vaccine Information Center Public Comment

Thank you for the opportunity to provide public comment today. Founded in 1982, the non-profit National Vaccine Information Center advocates for the institution of vaccine safety and informed consent protections in public health policies and laws. We support the availability of all preventive health care options, including vaccines, and the right of consumers to make educated, voluntary health care choices.

Meningococcal disease is devastating to those stricken and the public has a right to utilize Men B vaccines. As the committee considers routinely recommending Men B vaccines, please consider the following information.

The current U.S. population is estimated to be over 321[1] million, and according to the CDC, meningococcal disease in the U.S. ranges from 800-1,200 cases annually. A third of these cases are serogroup B,[2] with 60 percent of serogroup B cases occurring in children too young to benefit from Men B vaccines.[3] The CDC has also acknowledged that humans are the only natural reservoir for *N. meningitides,* and that as children grow to adulthood the vast majority will have bactericidal antibodies against this disease.[4]
Additionally, a CDC report published in 2000 revealed that routine recommendation of meningococcal vaccines for college freshman living in dormitories was not cost-effective. The report stated it would take 300,000500,000 doses of vaccine annually to prevent 15-30 cases of disease and one to three deaths. The costs were $600,000 to $1.8 million to prevent one case of disease, and $7 million to $20 million to prevent one death.[5] Although this report is precedes licensure of Men B vaccines, Men B vaccine cost-effectiveness findings would be similar. Because ACIP's routine recommendations often translate into legal vaccine mandates in many states,[5] choice and recommendations versus vaccine requirements were unifying themes noted in the CDC's 2011 stakeholder report on meningococcal vaccines.[6]
We have listened with deep sympathy to experiences shared by parents, whose children and families been devastated by invasive meningococcal disease. During ACIP meetings and the CDC's 2011 public engagement on meningococcal vaccines, some parents said their health care

[1] U.S. Census Bureau. U.S. & World Population Clock.
[2] CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases The Pink Book: Course Textbook.13th Edition (2015). CDC updated Jun. 17, 2015.
[3] Ibid
[4] CDC. Manual for Surveillance of VPD: Chapter 8: Meningococcal Disease. CDC updated Apr. 1, 2014. [5] CDC. Meningococcal Disease and College Students: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* - 49(RR07;11-20). Jun. 30, 2000.
[5] National Conference of State Legislatures (NCSL). Meningitis Laws at a Glance. NCSL updated 2012.
[6] CDC. Engagement Project Report: Meningococcal Vaccines and Infants/Toddlers. Executive Summary. Summer 2011.

providers did not make them aware of meningococcal vaccine availability. These parents had a right to know about the benefits and risks, and availability of meningococcal vaccines so they could make an informed decision for their children.

However, with regard to ACIP recommending that all children get Men B vaccines, the data is clear that a universal use recommendation is not justified. It would have far reaching consequences that will be costly and unnecessarily burdensome to parents, adults and government agencies.

NVIC respectfully requests the ACIP to vote against a Men B vaccine universal use recommendation. We encourage the ACIP and CDC to revisit the stakeholder report and the need for greater flexibility in ACIP recommendations.

Lewis & Clark Public Health

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June 19, 2015
Stephanie Thomas
Advisory Committee on Immunization Practices
1600 Clifton Road N.E.
Atlanta, Georgia
30333

Dear Ms. Thomas:

I am writing on behalf of Lewis & Clark Public Health in Montana to encourage the Advisory Committee on Immunization Practices to broaden the meningococcal recommendation to include serogroup B immunization for adolescent students and college students.

Preventing the spread of meningitis is a priority of our community and raising awareness of the need to be vaccinated is a particular focus of our Health Department. Many young adults and their families have been impacted by this terrible disease. This will continue to happen unless more students have access to vaccinations.

It's important to point out that the FDA has expedited the approval of vaccines against meningococcal serogroup B because they acknowledge the growing concern and the importance of preventing outbreaks of the disease. However, in order for people to have access, it's critical that ACIP expands the recommendation.

Based on this, we urge your timely review and approval of a broad, recommendation for routine immunization against meningitis B so we are able to keep our youth and young adults safe and avoid another tragic outbreak.

Thank you for your consideration of this important request.
Sincerely,

Melanie Reynolds, M.P.H.
Health Officer, Lewis and Clark Public Health

Our mission is to improve and protect the health of all Lewis and Clark County residents.

Stephanie Thomas
Advisory Committee on Immunization
Practices 1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas

The Osteopathic Physicians and Surgeons of Oregon (OPSO) represents over 1,300 physicians, residents, and medical students in Oregon. As part of our mission is to ensure the highest quality health care to the people of Oregon, OPSO strongly supports increasing immunization rates among Oregonians. Vaccinations against diseases such as bacterial meningitis are one of the most significant public health achievements of our time.

To achieve increased immunizations, OPSO encourages the Advisory Committee on Immunization Practices to consider adopting recommendations requiring meningococcal serogroup B immunization for adolescent and college students. As you know, a number of college campuses have recently experience outbreaks of serogroup B meningococcal disease. A recommendation from ACIP requiring immunization would be a significant step in preventing the death and disability brought on by an outbreak.

We hope you will address this issue at your upcoming meeting. I and the OPSO Board of directors would be happy to discuss with you in greater detail if you have any questions. Thank you for your kind consideration.

Sincerely,

David Walls
Executive Director
4380 SW Macadam Ave., Suite 185 | Portland OR 97239 | p: 503.299.6776 f: 503.241.4856

Thomas, Stephanie B. (CDC/OID/NCIRD)

From: Peter E. Johnsen, M.D. <johnsenp@Princeton.EDU>
Sent: Friday, June 19, 2015 3:39 PM
To: Advisory Committee on Immunization Practices (CDC)
Cc: Charlotte Treby M. Williams; Karen A. Jezierny; John Kolligian Jr.
Subject: MenB vaccine recommendations

Dear Members of the ACIP subcommittee on meningitis,

As you are aware, Princeton University experienced an outbreak of meningococcal B disease in 2013-14. There were 9 cases related to a unique outbreak strain. The CDC indicated that our attack rate was greater than 130/100,000. There was 1 death associated with this outbreak; 1 survivor is reported to have had hearing impairment, 1 survivor continues to have chronic daily headaches, and 1 survivor had cognitive impairment (which appears to have resolved after a number of months). Even one death is tragic; since we had several students in multi-system failure, we consider ourselves fortunate that the case-fatality rate was not even higher, and that we did not experience more residual effects.

As you know, our outbreak was not temporally clustered, but was sustained over a period of approximately one year. Of the 7 Princeton students involved, only one presented with symptoms considered typical of meningococcal disease.
Other presentations:

- One presented with a sore throat, was placed on penicillin. He was aware of our meningitis outbreak and asked to be reevaluated 12 hours later because he was concerned his situation was becoming worse.
- One presented with report of a fever the night before but looked well on presentation in the morning and had only a low grade fever. Because of our awareness of meningococcal disease on campus we observed her in the Infirmary; when her white blood count returned elevated we sent her to the Emergency Department at a nearby hospital. A short time later she developed a typical rash.
- Another student presented with fever, exudative tonsillitis, and a positive rapid strep test. We observed him in the Infirmary and, in the middle of the night, he developed the classical purpuric rash.
- This is not an easy disease to detect early in a student population. Our experience has been that our students appeared to compensate fairly well over the first 12-18 hours, and then had a sudden precipitous drop. Establishing an alternative diagnosis, such as streptococcal tonsillitis or influenza, does not exclude meningococcal disease. Most colleges and universities do not have the ability to monitor patients overnight. The vast majority of meningococcal cases are sporadic, which means that clinicians will not have the high index of suspicion that we developed during our outbreak.

Despite an aggressive hygiene campaign, we continued to see cases every few weeks in the Fall of 2014. We initiated a vaccine campaign in December 2014 under an Investigational New Drug

protocol. We ultimately achieved approximately 98% first dose (and 94% second dose) coverage of our undergraduate body. We had no subsequent cases among our students. There was one additional case involving a student at another university who had had contact with Princeton students, suggesting asymptomatic nasopharyngeal carriage persisted and herd immunity was not established.

Vaccine cost will factor in to any decision process. The cost to a university of a case of meningococcal disease can be enormous. While there are costs in terms of human suffering and direct medical / vaccine costs, there is also the cost associated with developing an infrastructure on the fly to cope with a possible outbreak. There is a cost in the enormous number of person-hours invested in dealing with an outbreak and the level of public anxiety. There are opportunity costs associated with diversion of medical and other resources. Costs cannot simply be measured in terms of quality life years saved.

1

It seems anomalous that, in New Jersey, incoming residential college students are required by law to have documentation of meningococcal ACYW vaccine, and are not allowed to register for classes if they cannot provide documentation, but for meningococcal B disease, which constitutes as significant a threat, there is no recommendation.

I have informally reviewed much of what I've written here with several member of the subcommittee in the past. I recognize that there are remaining technical questions about the vaccine in terms of breadth of coverage against different strains, effect on nasopharyngeal carriage, and duration of protection. These questions obviously must be addressed. I also recognize that cost is a major factor that must be considered. However, given that meningococcal disease is difficult to diagnose on a campus in the stage at which it is most curable, and that current recommendations do not address preventing the majority of cases (primarily sporadic), I do not see alternatives to vaccination if we are to prevent the tragic outcomes of this disease. I would urge that you support a strategy that would allow insurance coverage of this vaccine, as for other preventive vaccines.

Peter Johnsen, MD
Director of Medical Services
Princeton University

CDC's Advisory Committee on Immunization Practices
Jonathon Temte, MD, PhD, Chairman

Dear Dr. Temte,

My daughter, Jacquelynn Ross, will be providing public comments at Wednesday's ACIP meeting regarding our family's struggle to obtain the Meningitis Strain B vaccine for her. I wanted to reiterate some of the troubles that our family encountered over the last six months since the first of the MenB vaccines came onto the market.

Since last- December when Pfizer's MenB vaccine was introduced for public use, and then again in March when Novartis rolled out their vaccine, we have worked with both of these drug manufacturers trying to get one of these vaccines into our pediatrician hands so that Jacquelynn could receive the vaccination. We have already lost one daughter to the Meningitis Strain B bacteria and did not want to lose the other one.

After many calls, emails and countless days of waiting for a response from the drug companies and more importantly from our pediatrician's practice, the end result was that our pediatrician's practice could not acquire the MenB vaccine. Whether this was a decision made by the doctors in charge of the practice or more likely by the health care provider network that the practice is a part of, the bottom line was that our pediatrician was basically blocked from getting the MenB vaccine to give to Jacquelynn.

But we didn't give up there. At the suggestion of our pediatrician we then attempted to acquire the vaccine on our own through various pharmacies. The popular retail outlets told us they could not get the MenB vaccine and when we finally did find a pharmacy that could get it, the pharmacy did not have anyone on staff that could administer it.

It was an extremely frustrating process. We finally found a travel vaccination clinic that could order the vaccine and also administer it. We went this route because we were motivated to get our remaining daughter vaccinated. I am fairly certain, however, that some other parents will not be comfortable having to go to such a clinic (assuming one is even available) that is:

- located in an off the beaten path office park
- housed in a sparsely furnished one room office
- only open three days a week
- staffed by a receptionist/office manager/nurse/janitor

in order to get this vaccine to protect their children. This vaccine needs to be available in a more mainstream manner so that more of our children are protected from this devastating disease.

I ask that you please keep my daughter Stephanie, who died while attending Drexel University, and all of the others who have died most recently from the MenB bacteria in your thoughts as you prepare to vote on a level of use of the MenB vaccines. We are hopeful that the committee will vote for broad-based use of the MenB vaccines so that our nation's youth will be protected from the truly terrible disease.

Thank you for your consideration.

Stephen M. Ross

The Federation of Independent Illinois Colleges and Universities

Adler School of
Professional Psychology
Augustana College
Aurora University
Benedictine University
Blackburn College Bradley University
Chicago School of
Professional Psychology
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Saint Xavier University
School of the Art Institute
Shimer College
Trinity Christian College
Trinity College of Nursing
Trinity International University
University of Chicago
University of St. Francis
VanderCook College of Music
Wheaton College

June 22, 2015

Larry K. Pickering M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333
Via: Email PDF

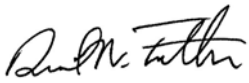
Dear Dr. Pickering,

As the president of the Federation of Independent Illinois Colleges and Universities, I respectfully write to urge the Advisory Committee on Immunization practices (ACIP) to endorse at its June 2015 meeting routine recommendations for the immunization of adolescents and college-age students against serogroup B meningococcal disease.

As an advocacy organization that represents over 200,000 students, as well as over 60,000 employees, we are understandably concerned about meningitis B given the high risk age cohort and environment (dorms and apartments) unique to our students. The availability of these vaccines for students as soon as possible will help to minimize the possibility of future tragedies similar to the outbreaks experienced by a number of college campuses across the country.

The Federation of Independent Illinois Colleges and Universities is the oldest private college association in the nation. The Federation is an advocacy organization that represents the public policy interests of Illinois' non-profit colleges and universities. With a membership of sixty institutions from all regions of the state, the Federation is the unified voice on behalf of the independent not for profit sector of higher education in Illinois.

Thank you for your consideration, and the work that you do to secure the health of our citizens.
Regards,



David W. Tretter
President

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Healthier Colorado
1536 Wynkoop St., Suite 109
Denver, CO 80202

Dr. Tom Frieden
Director, Centers for Disease Control & Prevention 1600
Clifton Rd.
Atlanta, GA 30329

Dear Dr, Frieden,

Healthier Colorado is a nonpartisan, nonprofit organization dedicated to ensuring that the voices of all Coloradans are heard by our public officials on issues concerning health. We believe every Coloradan should have access to the basic elements of healthy living. We believe immunizations are a vital tool to keep our communities safe and healthy, and the federal list of recommended vaccines has a major impact on who has access to these vaccines.

We, the undersigned, urge the federal Advisory Committee on Immunization Practices to formally include the meningitis B vaccine on the list of recommended vaccines for Americans. This is a common-sense suggestion that will reduce the risk of outbreaks on college campuses and save lives.

One fifth of all meningococcal infections occur in young adults between the ages of 14 and 24, and college students are at particularly high risk because dormitories are ideal environments for spreading this disease. Over the past months, we have seen the danger of not vaccinating. Six students and one parent of a student from the University of Oregon contracted the disease this year, resulting in the death of one student athlete in February. Other colleges and universities such as Princeton, Yale, Providence College, Oregon State and UC Davis have also experienced outbreaks of meningitis B. And these outbreaks are very serious. According to the CDC, the fatality rate of this disease is between 10 and 15 percent. Even with recovery, 19 percent of those affected suffer from complications, including severe damage to the nervous system, deafness, brain damage and loss of limbs.

The FDA licensed the meningitis B vaccine in October 2014, and doctors agree that it is perfectly safe. Other countries, including Canada, Australia, and several European nations recommend meningitis B vaccinations for all young adults. By making this simple change to the ACIP list of recommended vaccines, we can save lives and reduce medical costs. We urge the ACIP to make this change.

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Boulder, CO 80303

Marlene Waite
6979 S. Elk Ct
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Susan Welty RN
372 Silver Circle Dr
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10355 Dover St Apt 1416
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11953 Clay Ct
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Venis White
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Westminster, CO 80031

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2535 Race St
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Jacob Williams
2024 Clipper Dr
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Jeanette Williams
3610 Race St
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648 Laredo St
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14945 Foothill Rd
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2501 E104 Ave
Denver, CO
80233

UNM DIVISION of STUDENT AFFAIRS

Student Health & Counseling (SHAC)

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Dr. Pickering,

In advance of the upcoming meeting of the Centers for Disease Control Advisory Committee on Immunization Practices (ACIP), I am writing on behalf of the University of New Mexico Student Health and Counseling to urge ACIP to consider adopting a broad recommendation for the immunization of adolescents and college-age students against serogroup B meningococcal disease.

I have watched the recent outbreaks of meningitis B on campuses around the country with concern. I know that the members of ACIP will have all of the data on the epidemiology of meningococcal disease, as well as on the efficacy of the two recently approved vaccines against serogroup B meningococcal disease, and will take all that data into consideration.

I ask that the ACIP take into account the current recommendations for immunizations against Type A, C, W, and Y, and allow for consistent messaging regarding meningitis immunizations for college students. Also, the link between ACIP recommendations and health insurance coverage of the vaccine cannot be disregarded. Income disparities in utilization, thus protection, will increase, if such a costly vaccine must be paid out-of-pocket, for entering college students and their families.

I appreciate the work that the ACIP does in evaluating new vaccines and their potential contributions the health of the population. Those of us working in Higher Education are very concerned about the safety and health of college students and the campus community.
I appreciate the committee's consideration of this important issue.

Thank you.

Sincerely,

Beverly Kloeppel, MD, MBA
Executive Director, Student Health and Counseling
University of New Mexico
bkloeppe@unm.edu
505-277-1068

Confederation of Meningitis Organisations Committed to preventing meningitis worldwide, because we can and we should.

Administrative Address:
100 Roberts Road, Subiaco, Western Australia 6008
PO Box 855, West Perth, Western Australia 6872
Phone +61 8 9489 7791
comomeningitis@ichr.uwa.edu.au
www.comomeningitis.org

June 24, 2015

To the members of the Advisory Committee on Immunization Practices (ACIP):

Thank you for your hard work and dedication to making our world better by advancing sound immunization practices to protect your citizens against preventable illness and death. The Confederation of Meningitis Organisations (CoMO) joins with you in that goal, and is dedicated to preventing meningitis globally by ensuring families worldwide have access to early diagnosis, preventative measures, and quick treatment.

Approximately one-third of meningococcal disease cases in adolescents in the US are caused by serogroup B. Adolescents and young adults have the highest incidence of carriage in all age groups and are most vulnerable. They also interact with siblings and put younger children and babies at risk in the roles of helpers and babysitters. Please use your knowledge, the evidence, and your power to help us prevent meningitis from affecting others by recommending a routine vaccination against serogroup B meningococcal disease, making true and broad protection for teens a reality. We need you to take this step to fully cover the majority of people who want to protect themselves and their children from meningitis which, as you know, can kill or disable in hours.

In essence, our goal is to prevent meningitis worldwide because we can and we should. As individual members of CoMO, we unfortunately know first-hand the devastating effects of meningitis. Imagine losing your child or watching them become disabled for life to a vaccinepreventable disease, knowing that a vaccine was available. Although meningitis cases are relatively rare when compared to other diseases, the effects have been devastating to many. No one can put a price on the life of a human being, especially a child with the potential for a bright future.

We applaud the action taken by health authorities in the UK and Canada to protect the vitality and possibility of teenagers and young adults in their nations. Surely if there is help at hand, you would take this step? CoMO strongly urges you and your ACIP colleagues to follow the path created by the U.S. Food and Drug Administration in recommending the meningococcal B vaccine. Our children and young people deserve a full and fighting chance to live long and healthy lives.

Together, we must *Join Hands Against Meningitis*. We – the 43 member organisations of CoMO and in particular the 8 US-based organisations – are counting on you.

Thank you,
The Confederation of Meningitis Organisations

p 503 775 3497

10117 SE Sunnyside Rd.
Suite F-408
Clackamas, OR 97015

one in four
chronic health

June 23, 2015

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Ms. Thomas,

One behalf of One in Four Chronic Health, a collaborative organization working to support advocacy and access to affordable healthcare, I am writing to share our concerns regarding clusters of **invasive meningococcal disease** (IMD) among gay men, and men who have sex with men (MSM). We are particularly concerned prevention and treatment of the disease in HIV positive people, who have an increased risk of serious and sometimes fatal, complications.

We have seen clusters in a number of cities including New York, Los Angeles, San Francisco and Chicago and recently at the University of Oregon. Our concern is the increased number of recent clusters in men who identify as gay, and men who have sex with men (MSM), and the impact of IMD on HIV positive individuals.

The airborne particles of Meningitis B in respiratory fluid and can easily transmitted by **passing saliva or other membranous material between mouths and/or noses, in acts such as kissing or sneezing. Combined with an incubation period of up to one week without symptoms makes prevention difficult to impossible.**

Patients with pre-existing medical conditions like HIV are at increased risk of complications and death. Epidemiological data from clusters in New York City shows more than half (55%)[i] of patients were HIV positive. A 2014 study published in the Annals of Internal Medicine[ii] looking at New York data concluded "**people living with HIV/AIDS in NYC are at increased risk for IMD.**" The study found that among HIV positive meningitis patients were 5.3 times more likely to have CD4+ cells of less than 200 cells/mm3, dramatically increasing their risk of progression to AIDS and death.

For these reasons that we support expanding Meningitis b vaccination access for gay men and MSM's as a part of a larger public health program to identify and treat communicable disease.

Thank you for the opportunity to share our comments with you. If you should have any questions, please contact me at 206/601-8453.

Sincerely,

BJ Cavnor,
Executive Director

a voice for patients
1-in-4.org

[i] Hall, Chris D, MD, *The Facts About Bacterial Meningitis for Gay Men in San Francisco*, San Francisco AIDS Foundation http://www.sfaf.org/hiv-info/hot-topics/from-the-experts/the-facts-about-meningitis.html

[ii] Laura Miller, MPH et al. *Elevated Risk for Invasive Meningococcal Disease Among Persons With HIV* Annals of Internal Medicine, January 7, 2014 Vol 160, No. 1, http://annals.org/article.aspx?articleid=1763213

University of Idaho
A LEGACY OF LEADING
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June 23, 2015

Dr. Larry Pickering, Executive Secretary, ACIP
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering,

On behalf of the University of Idaho, I would like to add my support to requests that the Advisory Committee on Immunization Practices (ACIP) adopt recommendations for meningococcal serogroup B immunization for adolescents and students of college age.

Recent health threats on college campuses--including incidences of meningococcal serogroup B at one of our regional neighbors, the University of Oregon--highlight the value of immunization. Due to the shared living environments at dormitories, apartments, and fraternity and sorority houses, college students are particularly at risk in the face of public health threats. We observe this reality at the University of Idaho, with most of our undergraduate students attending our institution as residents.

Currently, the State of Idaho does not have a vaccination policy for attendees of higher education institutions, and I have proposed to our State Board of Education that we adopt such a policy. Drawing upon the ACIP work in making recommendations may inform and bolster any future state policies here in Idaho. A broad, routine recommendation may also facilitate insurance coverage of such an immunization, easing the cost for students and families and ensuring a more successful program of vaccinations.

Including meningococcal serogroup B vaccines in required vaccinations will protect the health of students at the University of Idaho, as well as community members in Idaho and across the region. We would be eager to collaborate with other institutions in Idaho and across the region to implement requirements.

Sincerely,

Chuck Staben

Chuck Staben
President

Thomas, Stephanie B. (CDC/OID/NCIRD)

From: Kimberly Coffey Foundation <kimberlycoffeyfoundation@gmail.com>
Sent: Tuesday, June 23, 2015 2:57 PM
To: Advisory Committee on Immunization Practices (CDC)
Subject: HIGH PRIORITY MENINGOCOCCAL SEROGROUP B VACCINE RECOMMENDATION

Dear Dr. Jonathan L. Temte and Dr. Cindy Weinbaum:

Below is my testimony from the Feb 2015 meeting:

Three years ago today, my 17-year-old daughter Kimberly Coffey from New York, should have graduated with her senior high school class. Instead she was buried 3 days earlier as she died from serogroup B meningococcal disease. I had the false sense of security that Kim was completely protected against this horrific disease when she was vaccinated with Menactra.

Unfortunately, I found this not to be true as I watched my healthy daughter die a terrible death from meningococcemia over the course of 9 days and ultimately be declared brain dead.

Serogroup B vaccination would have saved my daughter's life if it had been available.

Please make these vaccines available to all instead of only to limiting to college outbreaks and patients with complement deficiencies.

https://youtu.be/WFcQzl4qFFQ

Sincerely,

Patti Wukovits, R.N.
Executive Director
Kimberly Coffey Foundation
PO Box 344
Massapequa Park, NY 11762
www.kimberlycoffeyfoundation.org
(516) 982-1433

Ms. Stephanie Thomas June 23, 2015
Advisory Committee on Immunization
Practices Centers for Disease Control and
Prevention 1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas:
On behalf of the membership of The Wall Las Memorias Project, I strongly urge the Advisory Committee on Immunization Practices to consider recommending broader meningitis vaccination for youth and LGBT populations, especially those living with HIV.

There is no doubt that those who are at risk for HIV are more likely to contract meningitis B. From various reports, young people living in close proximity, such as college, university dorms are also at risk. The most vulnerable are those from underserved, homeless and immigrant populations. Due to economic status many of our people have to love in close living quarters and this is often a breeding ground for meningitis.

The Wall Las Memorias Project has provided HIV prevention and testing services to the Latino and LGBTQ community and have fought for better health care coverage for our people.

Today, the Advisory Committee can contribute greatly to improving the quality of life for millions of Californians.

Thank you,

Richard Zaldivar
Executive Director

5619 Monte Vista St., Los Angeles, CA 90042 * P-323-257-1056 * F-323-257-1095 * www.thewalllasmemorias.org

June 22, 2015

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, NE
Atlanta, GA 30333

Re: Recommendation for meningitis B immunization

Dear Ms. Thomas:

We are members of the Health Policy Council, which is a network of physicians who also serve as legislators in statehouses across the country. The Health Policy Council is sponsored by the Alliance for Patient Access*. As legislators, we have a vested interest in the safety of higher education in our respective states. As physicians, we recognize the importance of vaccination against preventable disease and protection for public health.

Therefore, in our capacity as both lawmakers and health care providers, we urge the Centers for Disease Control and Prevention to adopt a comprehensive recommendation for immunization against serogroup B meningococcal disease.

Meningitis B accounts for the majority of bacterial meningitis cases in adolescents, according to the National Foundation for Infectious Diseases. As the CDC recognizes, the disease disproportionately affects college students who often live in close quarters at university dormitories.

But while the Food and Drug Administration recently approved two meningitis B vaccines, many students do not yet get immunized against this strain of meningitis. Adding the vaccine to the standard schedule of immunization would increase the likelihood of students receiving it, improving university populations' safety and health.

College students embody our states' bright futures, and they deserve to be protected against preventable death and disability. Thus, at the June meeting of your Advisory Committee on Immunization Practices, please opt to comprehensively recommend the meningitis B immunization. By doing so, you can help to shield college campuses from disease outbreaks and ensure that students across the nation do not unnecessarily face this deadly disease.

Sincerely,
Alliance for Patient Access
Health Policy Council members

State Representative Jim Neely, D.O.
Family Practice
Cameron, Missouri

State Senator Tom Takubo, D.O.
Pulmonology/CCM
South Charleston, West Virginia

State Senator Elizabeth Steiner Hayward, M.D.
Family Medicine
Portland, Oregon

State Representative David Watkins, M.D.
Family Medicine
Henderson, Kentucky

*The Alliance for Patient Access receives financial support from a broad range of associate members, donors, and sponsors including Pfizer, Inc. and GlaxoSmithKline plc, both manufacturers of meningitis B vaccines.

Alliance for Patient Access
2000 M Street NW, Suite 850
Washington, DC 20036
http://allianceforpatientaccess.org/health-policy-council/

NEVADA STATE COLLEGE
bold. great. State.

May 29, 2015

Stephanie Thomas
Advisory Committee on Immunization Practices (ACIP)
1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas:

As Dean of the School of Nursing at Nevada State College, I write to urge the Advisory Committee on Immunization Practices (ACIP) under the auspices of the Centers for Disease Control (CDC) to adopt at its June 2015 meeting a broad, routine recommendation for immunization of adolescents and college-age students against serogroup B meningococcal disease.

As you know, a number of college campuses across the country have recently experienced outbreaks of serogroup B meningococcal disease. According to the National Foundation for Infectious Diseases, meningitis B is now the most common cause of meningococcal disease in adolescents. This is most likely because an increasing number of students are being vaccinated against other strains of meningitis, but not meningitis B.

Fortunately, the Food and Drug Administration (FDA) recognized the threat of meningitis B and fast-tracked the approval of vaccinations to prevent the disease. CDC recommendations for the meningitis B vaccine will be a huge step toward ensuring that college students and others at risk are protected against this fast-moving and often fatal illness. Health providers rely on CDC recommendations to determine which patients need which vaccination.

Vaccinations against diseases like bacterial meningitis are one of the most significant public health achievements of our time. When it comes to this and other infectious diseases, no treatment is more effective than vaccination.

As a college leader, I am particularly concerned about meningitis B because one-fifth of all meningococcal infections occur in young adults between the ages of fourteen and twenty-four, and college students are especially at risk because dorms and apartments are the ideal environments for spreading the disease.

School of Nursing
303 S. Water Street, Henderson, Nevada 89015
P: 702-992-2850 | F: 702-992-2851 | nsc.edu

Moreover, without a broad, routine recommendation, insurers typically will not cover a vaccination, meaning only those who can afford to pay out of pocket for the vaccine will be protected. Surely inculcating this kind of disparity is not consistent with the CDC's mission of protecting the public health.

We must make these vaccines available to all our students as soon as possible, before another tragedy strikes that we could have averted.

Thank you for considering this request, and for all that you, the ACIP, and the CDC do to increase the health security of our nation.

Sincerely,

Neal Rosenburg, PhD, RN
Dean

UNIVERSITY OF HOUSTON SYSTEM
UNIVERSITY OF HOUSTON

RENU KHATOR
Chancellor and President

June 11, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

The University of Houston System encompasses three universities and teaching centers in the Greater Houston metropolitan area, and one university in Victoria, Texas. As system chancellor, I am responsible for the education and well-being of more than 68,000 students.

I write today out of concern that, according to the CDC, the fatality rate of meningococcal disease is an alarming 10 to 15 percent – even when the patient is treated swiftly. I know that a number of universities have recently experienced outbreaks of serogroup B meningococcal disease, putting thousands of students at risk.

Of particular concern is the fact that one in five of all meningococcal infections occur in young adults between the ages of 14 and 24. College students are part of this age group, and they are especially at greater risk because on- and off-campus student dorms and apartments are ideal environments for the spreading of the disease. At the flagship University of Houston alone, close to 8,000 students live on campus and nearby housing – we have the second highest residential student population in Texas.

I encourage the Advisory Committee on Immunization Practices (ACIP), under the auspices of the Centers for Disease Control, to adopt at its June 2015 meeting a broad, routine recommendation for the immunization of adolescents and college-age students against serogroup B meningococcal disease. I am advised that, without this recommendation, insurers will not typically cover a vaccination, with the result that only those who can afford to pay will be protected. If that is the case, many of our students who come from first-in-college families and difficult financial situations will not be able to receive the vaccine, putting them and all those around them in danger.

212 E Cullen Building • Houston, Texas 77204-2018 • 713.743.8820 • Fax: 713.743.8837

We respectfully ask that ACIP act quickly with all means within its power to make the vaccine available to all students as soon as possible. I thank you, on behalf of our students, for your consideration.

With warm regards,

Renu Khator

Renu Khator

cc: William Staples, President, UH-Clear Lake
William Flores, President, UH-Downtown
R. Victor Morgan, President, UH-Victoria
Jason Smith, Vice Chancellor for Governmental and Community Relations, UH System

OPSO
OSTEOPATHIC PHYSICIANS & SURGEONS OF OREGON

Stephanie Thomas
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E.
Atlanta, GA 30333

Dear Ms. Thomas

The Osteopathic Physicians and Surgeons of Oregon (OPSO) represents over 1,300 physicians, residents, and medical students in Oregon. As part of our mission is to ensure the highest quality health care to the people of Oregon, OPSO strongly supports increasing immunization rates among Oregonians. Vaccinations against diseases such as bacterial meningitis are one of the most significant public health achievements of our time.

To achieve increased immunizations, OPSO encourages the Advisory Committee on Immunization Practices to consider adopting recommendations requiring meningococcal serogroup B immunization for adolescent and college students. As you know, a number of college campuses have recently experience outbreaks of serogroup B meningococcal disease. A recommendation from ACIP requiring immunization would be a significant step in preventing the death and disability brought on by an outbreak.

We hope you will address this issue at your upcoming meeting. I and the OPSO Board of directors would be happy to discuss with you in greater detail if you have any questions. Thank you for your kind consideration.

Sincerely,

David Walls
Executive Director

4380 SW Macadam Ave., Suite 185 | Portland OR 97239 | p: 503.299.6776 f: 503.241.4856

NORTHERN ARIZONA UNIVERSITY

Campus Health Services
Medical Services

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Flagstaff, AZ 86011-4101

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June 9, 2015

Larry K. Pickering, M.D.
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

I am writing, as the lead Public Health official at Northern Arizona University, to request that the Advisory Committee on Immunization Practices (ACIP) adopt recommendations for the immunization of adolescents, and particularly college-aged students, against serogroup B meningococcal disease that are in line with the ACIP and Centers for Disease Control and Prevention recommendations for vaccination against other serogroups of meningococcal disease when the ACIP next meets in June 2015.

I know that the members of the ACIP will have all of the data on the epidemiology of meningococcal disease, as well as on the efficacy of the two recently approved vaccines against serogroup B meningococcal disease, and will take all of that data into consideration in its decision making process. I am also aware that the ACIP evaluates and is sensitive to the cost effectiveness of any potential recommendation they make, as is appropriate for a group such as yours with the power to significantly impact not only the health of the U.S. population, but also U.S. healthcare expenditures. I would ask the members of the ACIP to consider that cost effectiveness should include an evaluation of the potential cost effectiveness of a vaccine with an ACIP recommendation in place (e.g. factor in the cost of insurer negotiated pricing and lower out-of-pocket expenditures of

those being vaccinated, as well as the savings from cases prevented with higher immunization rates). Given that front line health care professionals make vaccination recommendations based upon ACIP recommendations, and many of the major health insurance companies use the ACIP recommendations as a guide to their payment coverage decisions regarding immunizations, an ACIP recommendation can have a significant impact on the utilization of a vaccine and the out-of-pocket expenditures of U.S. citizens in regards to receiving important immunizations. If it is the hope that the recently approved serogroup B meningococcal vaccines, along with the meningococcal vaccines already recommended for use, can potentially reduce the incidence of serogroup B meningococcal disease specifically and meningococcal disease as a whole, then health care professional recommendations to get vaccinated along with health insurance coverage of the cost of those vaccines is going to be critical for supporting sufficient vaccine utilization to accomplish that goal.

I want to thank you in advance for your consideration of this perspective and sharing it with the members of the ACIP.

Sincerely,

Sandra Smith

Sandra Smith, M.D.
Interim Medical Director, Campus Health Services
Northern Arizona University

MICHIGAN STATE
UNIVERSITY

June 9, 2015

Larry K. Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

We are writing as the University Physician and Executive Director of Student Health Services for Michigan State University in support of adding serogroup B meningococcal vaccine to those immunizations routinely recommended for people 10-25 years of age. Recent outbreaks of serogroup B meningococcal disease at Princeton University and the University of California, Santa Barbara illustrate the potential harm caused by this vaccine-preventable disease on college campuses.

One would expect that the routine recommendation for administration of serogroup B meningococcal vaccine would decrease the current morbidity and mortality associated with this disease. The current use of this immunization primarily during outbreaks leaves our student population at risk for an eminently preventable and potentially catastrophic illness.

Thank you for your time and consideration of this important subject.

Sincerely,

David P. Weismantel, MD, MS
University Physician

Glynda Moorer MD, FAAFP
Executive Director, Student Health Services

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CMU CENTRAL MICHIGAN UNIVERSITY | College of Medicine

June 15, 2015

Larry K. Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Re: Meningococcal B

Dear Dr. Pickering:

Our country has some of the best medical care in the world; yet, we significantly lag the rest of the world in our public health and prevention initiatives. Immunizations are the cornerstone of public health, vaccines are safe and readily available but many of our children are under immunized. Over the past few years, many colleges witnessed outbreaks of preventable illnesses.

Meningococcal vaccine has been part of standard medical practice for several years and many colleges require it for their incoming students. Up until recently, this vaccine did not protect against the Type B strain. In 2014, the FDA approved a new version that protects against Type B meningococcus. A similar vaccine has been available in Europe for few years.

As the ACIP reviews it guidelines, I strongly recommend that you consider including coverage against Type B meningitis to protect our children and prevent unnecessary losses. I appreciate your consideration of this serious matter.

Respectfully,

George Kikano, M.D., Dean
Central Michigan University College of Medicine

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Central Values: Integrity | Respect | Empathy | Inclusiveness | Social Responsibility | Excellence | Innovation

UNT SYSTEM

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UNT Health Science Center
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OFFICE OF THE CHANCELLOR
Lee F. Jackson — Chancellor

June 15, 2015

Dr. Larry K. Pickering
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Dr. Pickering:

Over the past five years, universities across the country including the University of Oregon, Providence College, Princeton University, San Diego State University, the University of California - Santa Barbara, and Georgetown have come face to face with the devastating effects of meningococcal meningitis on their campuses. Some students lost limbs and some lost their lives.

This disease left its mark on Texas as well, resulting in the death of a Texas A&M University student in 2011 and the amputation of both legs of a University of Austin student in 2008.

The Food and Drug Administration recently approved licensing of two new vaccines which will protect against serogroup B, the most common strain of this disease in young people between the ages of 14 and 24. We strongly urge your committee to adopt a recommendation at your June meeting to include the serogroup B vaccination on the list of routine adolescent immunizations.

Adoption of this recommendation will increase the likelihood that our students and their families can receive health insurance coverage for this vaccine. It will also enable our institutions to require that all students be vaccinated against serogroup B prior to entering the classroom. It is a key step in protecting our campuses from this deadly disease.

Sincerely,

Lee F. Jackson, MPA
Chancellor, UNT System

Michael Williams, DO, MD, MBA
President, UNT Health Science Center

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Dallas, Texas 75201

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STUDENT LIFE
UNIVERSITY HEALTH SERVICE
UNIVERSITY OF MICHIGAN

Robert A. Winfield, M.D.
Director, University Health Service
Chief Health Officer, University of Michigan
rwinf@med.umich.edu

June 3, 2014

Larry K. Pickering, MD
Executive Secretary
Advisory Committee on Immunization Practices
1600 Clifton Road, N.E., Mailstop A27
Atlanta, Georgia 30333

Dear Dr. Pickering:

I am writing as the Chief Health Officer for the University of Michigan campuses to support the concept of broadening the indications for use of Meningococcal vaccines as a routine vaccination for college age students. This issue has particular importance for the college age population that has recently suffered a number of type B deaths in the recent past.

A broad, routine recommendation for the use of Meningitis B vaccine, versus the current limited use during type B outbreaks, will undoubtedly save lives, based on the same rationale that was used to broaden the use of the presently available meningococcal vaccinations. I believe there is some urgency to make a decisive recommendation prior to the beginning of the 2015 fall academic term that begins in September, in order to prevent avoidable disease, disability and death from this terrible disease.

I greatly appreciate your consideration of my viewpoint.

Sincerely,

Robert A. Winfield

207 Fletcher Street
Ann Arbor, MI 48109-1050

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FAX: 734-615-4777